

**SUSPENSION OF MEDICAL RESEARCH AT WEST
LOS ANGELES AND SEPULVEDA VA MEDICAL
FACILITIES AND INFORMED CONSENT AND PA-
TIENT SAFETY IN VA MEDICAL RESEARCH**

JOINT HEARING
BEFORE THE
SUBCOMMITTEE ON OVERSIGHT AND
INVESTIGATIONS
AND
SUBCOMMITTEE ON HEALTH
OF THE
COMMITTEE ON VETERANS' AFFAIRS
HOUSE OF REPRESENTATIVES
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SUSPENSION OF MEDICAL RESEARCH AT WEST LOS ANGELES AND SEPULVEDA VA MEDICAL FACILITIES AND INFORMED CONSENT AND PATIENT SAFETY IN VA MEDICAL RESEARCH

WEDNESDAY, APRIL 21, 1999

**HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS, AND
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON VETERANS' AFFAIRS,
Washington, DC.**

The subcommittee met, pursuant to notice, at 10 a.m., in room 334, Cannon House Office Building, Hon. Terry Everett (chairman of the subcommittee) presiding.

Present: Representatives Everett, Buyer, Stearns, Moran, McKeon, Brown, Gutierrez, Snyder, Rodriguez, Shows, and Doyle.

OPENING STATEMENT OF HON. TERRY EVERETT, CHAIRMAN, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

Mr. EVERETT (presiding). The hearing will come to order.

Good morning. This hearing will examine the suspension on March 22, 1999, of all medical research at the VA's West Los Angeles Medical Facility. We will also examine informed consent issues in VA medical research, generally.

After learning of the suspension of the research, Chairman Cliff Stearns of the Health Committee, and Ranking Democratic Member Corrine Brown of the Oversight and Investigations Subcommittee, and I were extremely concerned, and decided to have an expedited joint hearing. We wanted a public report on what happened, and what is being done about the situation. Obviously, the VA has failed to protect our veterans at the West Los Angeles Medical Research Facility. We know that much already.

The Subcommittee on Oversight and Investigations has been conducting oversight of VA patient safety issues as part of its oversight plan, and I regret to say that this is a major patient safety issue. This is the most serious trouble in VA medical research in many, many years. For the VA, the suspension is unprecedented. VA medical research is too important not to do it right. It has given veterans and all Americans many pioneering advances in medicine. We insist that the VA find out what the problems are, and correct them.

We also insist that those who are responsible be identified, and held accountable, something the VA has not been consistent in

doing. The issue before us today revolves around veterans given informed consent before participating in medical research. Without informed consent, no veteran can properly be a research subject. The concerns about informed consent go straight back to the awful things the Nazis did to people during the holocaust, and called it medical research. The civilized world vowed that it would never happen again, and in 1949 made a statement on the Nuremberg code to establish ethical guidelines for human medical research. I am deeply disturbed, and appalled by the report that four veterans at West Los Angeles VA were the victims of medical research without consent whatsoever. One of the veterans even refused consent. These veterans, who will not be publicly identified, were old and sick, and three out of four had psychiatric conditions. They were particularly vulnerable, and a VA doctor took advantage of them. Their faces are the faces of veterans in the VA hospitals across the country. The subcommittee demanded an explanation, and accountability. These outrageous crimes against our veterans must not happen again.

Our witnesses today are from HHS Office for Protection from Research Risks, from the VA's Washington office, and from the West Los Angeles VA. Also, we have a panel of experts in medical research anxious to give us their evaluation. At this time, I will recognize the distinguished Chairman of the Subcommittee for Health, Mr. Stearns.

**OPENING STATEMENT OF HON. CLIFF STEARNS, CHAIRMAN,
SUBCOMMITTEE ON HEALTH**

Mr. STEARNS. Good morning, and thank you, Mr. Chairman. I think you have outlined the position of our two joint committees this morning. For many of us, it has been quite a disappointment to understand this because the VA has long prided itself on the quality of its medical research program. In fact, a few of us went over to tour the Washington Veterans' Hospital here, and met with the Assistant Chief of Staff for Research, Dr. Levine, and many of us felt there was a lot of good research being done there. But, of course, the revelations leading to today's hearing raise some very, very troubling questions.

It is natural to ask whether attention to patient protection is as lax at other VA centers as, apparently, it was at West Los Angeles. We don't know the answer to that question because for too long it appears research has operated under a so-called trust relationship. Obviously, this trust relationship broke down at one hospital that we know of.

VA officials have been on notice, though, of the potential for this problem. So, this should not be totally a surprise to them. A retired NIH official appearing before our committee in a 1994 hearing on VA radiation research testified to VA's very limited oversight of patient protections. Let me quote to you this morning, Mr. Chairman, what he said. "In the Department of Veterans Affairs, you have one part-time official who looks after the implementation of the regulations in all of the VA hospitals. That man works nights; he works weekends, but that is not enough. He needs a staff. There is no trained investigator in the Department of Veterans Affairs to inves-

tigate complaints. We only have two in the Department of Health and Human Services.”

Dr. Kizer has devoted considerable attention, during his tenure, to the issue of patient safety in VA facilities. So, many of us will be very anxious to hear from Dr. Kizer on the third panel.

Research, as all of us know, is a key VA mission, but obviously we need to safeguard the patients and make sure these safeguards are in place so that all patients are protected against undue risks in research.

So, Mr. Chairman, together with my staff, we commend you for this hearing, and we look forward to hearing from all the panelists. Thank you.

Mr. EVERETT. Thank you. I now recognize the ranking member of our Oversight and Investigations Subcommittee, Ms. Corrine Brown for an opening remarks she may have.

OPENING STATEMENT OF HON. CORRINE BROWN

Ms. BROWN. Thank you, Chairman Everett, and members of the committee. We all know that VA research has made major contributions to healthcare for veterans, and to healthcare in general. VA medical care, supplemented by VA research, is a significant part of any intelligent discussion of healthcare in America. VA research has produced major breakthroughs, including the pace-maker, the first kidney transplant in the United States, the CAT scan, and the MRI scan, the vaccination for hepatitis, the first successful drug treatment for TB, high blood pressure, and schizophrenia, lighter and more responsive prostheses for amputees, kidney, and home dialysis techniques. These are medical advances the whole world needs to be using today. There will be more.

Congress has faith in VA research. However, veterans check into the VA for care, not to give scientists help with experiments. When veterans at the VA agree to take part in experiments, the veterans should be helped. They must be the right subject, not merely the most convenient ones. Research at the West LA VA Medical Center appears to have crossed the line set forth in law and regulation. Congress will not tolerate this.

In addition, whenever an urban hospital performs life-endangering procedures on its patients without the consent, Congress must ask very serious questions. I am concerned that patients who are poor, who have no other recourse for medical treatment, and are heavily weighted toward minority population have become too available for experiments that may serve science, but not the veterans who have already given more than this Nation asked for.

The purpose of this hearing is to learn from what has happened in West LA and the rest of the Greater Los Angeles system—is West LA an exception or is it a glaring example of a system-wide problem? What assurances can VA give us that the situation in West LA is being corrected, and that requirements set forth in law and regulations are applied and enforced throughout the VA network? I believe these issues before us boil down to two questions: Are current research rules adequate for protecting veterans, including older and mentally ill veterans, and are the rules seriously in force? I look forward to getting some answers this morning. Thank you, Mr. Chairman.

Mr. EVERETT. Thank the gentle lady. Now, I recognize the ranking Democrat on the Health Subcommittee, Mr. Gutierrez, for any opening remarks he may have.

OPENING STATEMENT OF HON. LUIS V. GUTIERREZ

Mr. GUTIERREZ. Thank you, Mr. Chairman. I would like to thank the witnesses for being today, and I hope this hearing will give us the opportunity to find out what transpired at the Veterans Affairs Medical Center in West Los Angeles and Sepulveda.

I am deeply disturbed that the reports of veterans being exploited by staff at VA hospitals for research purposes. These are very serious allegations which suggest that doctors put aside their consciences and medical responsibilities to achieve personal gain. Thousands of veterans in this country rely on the VA for medical care and treatment. I recognize that many important medical advances have come from VA research. Many veterans welcome the opportunity to participate in medical research programs that offer them the most advanced treatment available. But if informed consent requirements for veteran patients are not respected, and researchers are not held accountable for their unethical research practices, VA research should cease to continue.

Much to my dismay, I believe the VA is in crisis, and that the problems identified at West Los Angeles and Sepulveda reflect larger problems, Mr. Chairman. As we know the Department of Veterans Affairs is facing a severe budget constraint. The lack of proper funding has led to the reduction of medical staff at VA hospitals by the thousands, and are projected in the coming year to be 7,500. It is not uncommon for a veteran to wait months to see a doctor for an examination or over a year to get treatment.

I also understand that some VA hospital administrators are receiving bonuses, Mr. Chairman, in their contracts, bonuses which are directly related to eliminating nurses, physician assistants, and medical staff because they are meeting the goals of cutting costs. I am very concerned that the severe budget crisis the VA is facing is responsible for creating a system where mistakes, abuse, and consistent inadequate care is the norm for our veterans.

In this specific case, if we find the patients were, in fact, used for research purposes by their doctors without consent, or in violation of strict medical regulations, we must hold those doctors accountable. We must also make every effort to ensure that if illegal and unethical violations were committed by medical staff, such crimes—I underscore the word "crimes,"—must never occur again at any VA facility. But the work must not stop there.

Patient care should be our most important priority. Mr. Chairman, the VA has many doctors and nurses who are dedicated to their jobs, and the patients they serve. Perhaps these men and women do not receive the recognition they deserve. However, this specific case should serve as a wake-up call for the entire system. Our VA healthcare system is failing our veterans. More funding, more programs, more oversight, and more dedication to our veterans is desperately needed. Thank you, Mr. Chairman.

Mr. EVERETT. Thank you. Dr. Snyder, any remarks you may have? If you care to submit something for the record, please do so. Mr. Moran?

Because of the nature of some of today's testimony, the witness panels will be sworn in for their testimony. I ask witnesses to please limit their oral testimony to 5 minutes. Your complete written statement will be made part of the official hearing record. I also ask that we hold all questions until the entire panel has testified.

At this time, I would like to recognize Panel I: Dr. Tom Puglisi, Director, Division of Human Subject Protections, Office for Protection from Research Risks, National Institute of Health in the Department of Health and Human Services, and ask him to please introduce his staff.

TESTIMONY OF J. THOMAS PUGLISI, DIRECTOR, DIVISION OF HUMAN SUBJECT PROTECTIONS, OFFICE FOR PROTECTION FROM RESEARCH RISKS, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES; ACCOMPANIED BY GARY B. ELLIS, DIRECTOR, OFFICE FOR PROTECTION FROM RESEARCH RISKS, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

TESTIMONY OF J. THOMAS PUGLISI

Mr. PUGLISI. Mr. Chairman and members of the subcommittees, I am Tom Puglisi, Director of the Division of Human Subject Protections in NIH's Office for Protection from Research Risks, OPRR. I am accompanied by Gary B. Ellis, OPRR's director. Dr. Ellis chairs the Inter-Agency Human Subjects Committee of which the VA is an active member, in the person of Dr. Tim Gerrity, whom you will hear from later this morning.

Mr. EVERETT. Dr. Puglisi, will you please repeat after me?

[Witness sworn.]

Mr. EVERETT. Thank you. Please go ahead.

Mr. PUGLISI. This spring marks the 25th anniversary of the 1994 Department of Health and Human Services Regulations for Protection of Human Subjects. In 1991, the core HHS regulations were adopted by other departments and agencies, including the Department of Veterans Affairs, as the Federal Policy, Common Rule, for the protection of human subjects. Today the Common Rule is shared by 17 departments and agencies covering most, but not all, Federally-sponsored human subjects research.

The Common Rule provides three key protections for human subjects: First, research must be reviewed and approved by a duly constituted Institutional Review Board. Second, researcher must obtain and document subjects' informed consent. Federal regulations require that informed consent include eight specific elements of information. Any researcher who recruit a subject without conveying all eight of these required elements is not obtaining informed consent. Third, research institutions must provide the Federal Government with a satisfactory Assurance of Compliance. An Assurance is a written commitment to adhere to basic ethical principles, and to the requirements of the Human Subjects regulations. Under the Common Rule, OPRR has authority to approve Assurances for Federal-wide use. Other Common Rule departments or agencies may approve Assurances for research that they themselves support.

From 1987 to 1998, the VA West Los Angeles and the VA Sepulveda held separate Federal-wide Assurances approved by OPRR. Upon their merger, OPRR approved a new Assurance for the VA Greater Los Angeles Health Care System which includes both facilities.

On March 22 of this year, OPRR deactivated that Assurance. What led to OPRR's action? In 1993, OPRR received an allegation that informed consent procedures for psychiatric research at West Los Angeles failed to meet regulatory standards. OPRR found numerous informed consent documents lacking basic required information, and ordered correction of these deficiencies.

In January 1995, I led a follow-up site visit to the West Los Angeles facility. The site visit revealed a number of serious deficiencies in the Institutional Review Board's operating procedures. OPRR required additional corrective actions. In April 1998, OPRR requested updated documentation regarding these required actions. Review of this information revealed continuing serious deficiencies in human subject protection procedures.

As a result, OPRR deactivated the VA Greater Los Angeles Health Care System Assurance. This action removed the Assurance required for conduct of Federally-supported human subjects research. HHS supported human subjects research may resume at the VA Greater Los Angeles Health Care System only under new Assurance mechanisms that entail more stringent oversight by OPRR.

As I indicated previously, OPRR has authority under the Common Rule for approving Assurances at HHS-supported institutions for Federal-wide use. At present, 41 VA facilities hold Assurances that are approved by OPRR for Federal-wide use. Some 50 VA facilities are covered under other Assurance mechanisms that are limited to specific categories of HHS-supported research.

OPRR is currently conducting three compliance investigations that involve other VA facilities, specifically the James A. Haley VA Hospital which is conducting research in association with the University of South Florida in Tampa, the Philadelphia VA Medical Center, and the Cincinnati VA Medical Center which is conducting research in association with the University of Cincinnati. I am not able to comment further on these ongoing investigations because OPRR has not yet reached any determinations of fact in these cases.

OPRR recently completed a complex investigation of several HHS-supported psychiatric research projects at the VA Medical Center in the Bronx, New York, research that was conducted with the Mt. Sinai Medical Center. Although deficiencies were identified, OPRR has now determined that appropriate corrective actions have been implemented for current and future research. OPRR has neither an immediate nor an historical basis for distinguishing compliance of VA medical centers as a class from that of other biomedical and behavioral research institutions.

It is clear, however, that VA medical centers have a profound obligation to ensure that our Nation's veterans are afforded the highest levels of protection when they become human subjects. To the extent that any VA research involves any veteran subject who may be vulnerable for any reason—for example, because of illness, eco-

conomic disadvantage, mental disability, because of institutionalization or for any other reason, the VA has a very special responsibility to provide particularly stringent protections. Thank you, Mr. Chairman. We are pleased to answer any questions you may have about safeguarding the rights and welfare of human subjects.

[The prepared statement of Mr. Puglisi appears on p. 95.]

Mr. EVERETT. Thank you very much for your testimony, and for appearing here today.

West LA is the first VA research facility to be actually suspended, is that correct?

Mr. PUGLISI. That is correct.

Mr. EVERETT. How many have been on probation in recent years, and which ones?

Mr. PUGLISI. I do not believe we have had other VA medical centers on probation in recent years, although we did conduct a long investigation of the psychiatric research at the Bronx VA. It wasn't actually on probation.

Mr. EVERETT. I will get to that in a moment, if you don't mind. What other research operations outside the VA have been suspended in recent years—outside the VA?

Mr. PUGLISI. Outside the VA, we have most recently suspended research at Rush Presbyterian Medical Center. We have also suspended certain classes of research at a number of other facilities over the past 10 years or so.

Mr. ELLIS. About 34 facilities have been either restricted or suspended by OPRR in some way through the last 9 years.

Mr. EVERETT. Last 9 years? Getting to the Bronx situation, what were the problems at the Bronx VA/Mt. Sinai you describe on page 8 of your testimony, were they similar to the West Los Angeles?

Mr. PUGLISI. In the case of the Bronx VA, we received allegations that informed consent documents failed to disclose the very serious risks related to certain psychiatric challenge studies that were being conducted there. We were also informed that informed consent documents, and the informed consent process didn't make clear that there might be alternatives to participating that might be beneficial to subjects. We essentially confirmed those allegations for a number of studies conducted at the Bronx VA, and required the Bronx VA and Mt. Sinai to institute corrective actions, not only in the informed consent process but also to establish some special oversight mechanisms for those types of very risky studies.

Mr. EVERETT. You are opening investigations into three other VA research facilities, Cincinnati, Philadelphia, and Tampa. What is the criteria for opening those?

Mr. PUGLISI. OPRR investigates any allegation of non-compliance that appears to be credible. If the complainant comes forward with specific allegations that name an institution, and characterize research well enough that we can identify it, we pursue that complaint.

Mr. EVERETT. The Long Beach, CA VA seems to relate to an OPRR restriction on research and drug addiction, a treatment being conducted by Dr. Walter Ling in Southern California. What can you tell the subcommittee about that?

Mr. PUGLISI. I can tell you that this research was funded through the Friends Research Institute on the west coast. We found that

the Institutional Review Board procedures that Friends was using failed to meet our standards. The Institutional Review Board did not consistently have a quorum or consist of members who were scientifically qualified to review the type of research that was being conducted. We also found that informed consent documents were not complete, and so forth. We took action against Friends to remove Friends' Assurance and require that research conducted through Friends be subject to special oversight by OPRR, which required that we review the protocols and informed consent documents ourselves after their Institutional Review Board had acted.

Mr. EVERETT. Was OPRR aware of the case of VA medical research at West LA to perform research on veterans without consent; and, was that a reportable situation under Federal Regulations; and, how did OPRR learn about the situation; how serious is it; and, finally, how could anyone allow that doctor to continue doing research on human subjects?

Mr. PUGLISI. I believe you are referring to the cardiology research that has recently received media attention. That research was not reported to us. We did not learn about it until we saw it in the media. It was reportable to us under the Assurance of Compliance that was in place at the VA at the time it occurred, so it should have been reported to us, and was not.

Mr. EVERETT. Can OPRR bar particular researchers from doing human research?

Mr. PUGLISI. OPRR cannot bar individual researchers from doing research. OPRR can prevent Department of Health and Human Services funds from flowing to an individual investigator to support research, but beyond the withdrawal of HHS funds, OPRR would have no jurisdiction over privately funded research or research funded by another agency that wasn't bound to an OPRR-approved Assurance.

Mr. EVERETT. I see my yellow light on, so we are going to have a second round for the members. At this time, I will ask Chairman Stearns for his questions.

Mr. STEARNS. Thank you, Mr. Chairman. Dr. Ellis, how long have you been in your present position?

Mr. ELLIS. Six and a half years.

Mr. STEARNS. Six and a half years. Dr. Puglisi has mentioned some of these problems dating back to 1993; were you on board at that time?

Mr. ELLIS. Yes, I was. I remember the initiation of the particular case at West Los Angeles, yes.

Mr. STEARNS. What was your feeling when you saw this?

Mr. ELLIS. Well, the initial allegation was linked with an ongoing case at the University of California Los Angeles, which involved schizophrenia research, and so it didn't come in isolation. It was weightier than a free-standing allegation—that is a term I am just inventing—and, so we took this very seriously. We know the institutions are located across the street from each other. We knew we had problems at UCLA; we know many investigators have joint appointments at the VA and UCLA, so it had a certain gravity to it. The case at West Los Angeles unfolded rather slowly. We did a site visit, Dr. Puglisi led it, in 1995. It was marked by non-responsiveness by the institution through months and years.

Mr. STEARNS. Well, Dr. Puglisi has pointed out that there is evidence of that VA medical centers in Tampa, Philadelphia, and Cincinnati have had similar problems. Doesn't that make you want to put in place a system to get some action here, and why wasn't that done?

Mr. ELLIS. Most important, as Dr. Puglisi noted, is that we don't have any basis either now or through the decade for distinguishing VA research facilities from all the biomedical and behavioral research facilities that we oversee. To the extent that our current system has gaps, our current system of oversight of VA facilities has gaps. I do think it is important to say we really can't distinguish VAs, as a class, as being better or worse than other places. We have a system of trust, and, as it has been characterized in the opening remarks as in question. That still appears to be the best system, the most reliable system we can manage, given the enormity of the biomedical and behavioral research enterprise, and the effort that the Government devotes to monitoring it.

Mr. STEARNS. You mention this system of trust, which is to protect the subjects from research risks. After what you heard in 1993, didn't it occur to you that, perhaps, you should set up routine auditing or compliance of regulations? Isn't that your responsibility?

Mr. ELLIS. Well, again, given the enormity of the research enterprise, the system that the Government has developed is based on trust. We extract a solemn promise from the institutions, we hold them responsible, and we investigate complaints. We have about 67 open investigations now; we do about three or four site visits a year. This is on a baseline of several thousand, 3,000 to 4,000 institutions, tens of thousands of projects, and an unknown number of human subjects. So, we do the best we can.

Mr. STEARNS. Well, you talk about this system of trust. Don't you rely on local institutional review boards for this trust? And isn't it often possible that these institutional review boards have conflicts of interest which would mean they couldn't oversee, or even provide the trust that you are looking for? Has that occurred to you? Is that true?

Mr. ELLIS. You characterize the system of decentralization correctly. The unit of governance here is the local committee to review the ethics of research. The regulations are quite clear that no member of an Institutional Review Board who has a conflict may take part in prospective review and approval. So, that issue is addressed.

Mr. STEARNS. Do you feel that the present protections in the current regulations are sufficient?

Mr. ELLIS. We have an excellent system of protection of human subjects, where it applies. The regulations do not extend to all. This is a surprise to many individuals. There is no statute in the United States that says for all human subjects in research, there must be prospective review by an Institutional Review Board, and there must be informed consent. The regulations cover, in our case, research funded or sponsored by the Department of Health and Human Services. The Food and Drug Administration has separate regulations that follow research that involves a drug, device, or biologic. But this is a patchwork system of protections that has a de-

fined perimeter, and there is no question we can see unchecked human experimentation beyond that perimeter.

Mr. STEARNS. Dr. Ellis, I had the opportunity to visit the Washington VA hospital, and talked with the Assistant Chief of Staff for Research, Dr. Levine. He actually showed me the consent forms, and Chapter 9 of the pertinent VA manual which set out what is required. So, it doesn't seem to me that it is ambiguous at all. It is concise; it is clear; it is methodical; it is there.

What we need is somebody to audit this. It seems to me, in your position, you should feel some concern that this trust relationship is not working because, although you say it is a patchwork, what I saw yesterday was very clear. So, I guess my final question would be, based upon the earlier testimony, is it your position today that we do not need to have any remedial steps taken to obviate these kind of problems? What are you recommending this morning; what are you telling all of us?

Mr. ELLIS. Given the system of trust that we have in place and the decentralized governance, I think the number one need is for education. This is preventive maintenance for the system.

Mr. STEARNS. Education of whom?

Mr. ELLIS. Education at every level—of institutional officials, the people at the very top; of Institutional Review Board members; of research staff; and of research investigators. So, there is virtually no upper limit to the amount of education that can be done or that is needed. Education is preventive maintenance for this system.

Mr. PUGLISI. I would like to add that I think the biggest threat to this system is the lack of resources that institutions provide to their institutional review boards. We noted a lack of resources at the West LA VA. We pointed out the lack of resources repeatedly to the West LA VA, and were never able to get a commitment from them for increased resources for their IRB. This is not a problem that is restricted to VAs. By and large, across the country, you will find that most institutional review boards are under-funded and under-staffed. It is largely a volunteer effort. I believe that a volunteer effort may have been appropriate 25 years ago when the system was established. Clearly, the volume and complexity of research that is being conducted today requires something more than a volunteer effort with few resources for operation. The biggest threat to the system, I think, is a lack of resources to support it.

Mr. STEARNS. Thank you, Mr. Chairman.

Mr. EVERETT. We will have a second round if you have additional questions. At this point, I would like to recognize the ranking Democrat on the Investigation and Oversight Subcommittee, Ms. Brown.

Ms. BROWN. Thank you, Mr. Chairman. I appreciate your testimony, and have a few questions to the panel. Are elderly veterans suitable subjects for medical experiment, and what limits do we need?

Mr. PUGLISI. Elderly subjects, certainly, can be suitable for biomedical research. However, elderly persons may be vulnerable to coercion or undue influence. Therefore, to the extent that older persons are vulnerable, special protections need to be taken to make sure that they, first of all, understand that they are being asked to engage in research. Extra steps should be taken to make sure

that the older subject comprehends that she or he is a research subject or is being asked to be a research subject.

Secondly, there should be monitoring in place to make sure that the older subject continues to understand the processes and risks involved in the research, and to understand that she or he has the option not to participate if she or he does not want to participate.

For vulnerable populations, such as elderly people, institutional review boards need to make sure there are special protections in place to ensure that subjects understand, and to ensure that the research is conducted in a safe manner.

Ms. BROWN. Is it appropriate, from the patient's standpoint, to ask them to go off their medication, and even a chance of getting a placebo, a sugar pill, for experimental purposes?

Mr. PUGLISI. It may be appropriate, under certain circumstances. What is critical, however, is that the subject understands exactly what the procedures are to be.

First of all, that withdrawal of medication entails great risk. That the probability of those risks is communicated very specifically to the subject. Secondly, the individual must understand that this is an entirely voluntary undertaking, and that there may be alternative medications that would be as effective or more effective than would be received in the research being conducted. Withdrawal of medication may be appropriate only when the subject fully understands what is going to be done, and what the risks are.

Ms. BROWN. Let me just ask you, is OPRR adequately funded, staffed?

Mr. PUGLISI. OPRR oversees research at approximately 4,000 institutions. We have our human subject staff of approximately 15 professional and support staff. We have two full-time professionals who conduct compliance oversight investigations.

Ms. BROWN. And you are overseeing what, 1,000?

Mr. PUGLISI. Roughly 4,000 institutions.

Ms. BROWN. You couldn't be doing an adequate job.

Mr. PUGLISI. We do the best we can do. We try to juggle the many cases that we receive, as well as our education and Assurance responsibilities.

Ms. BROWN. Do you think the VA needs to put more of its research dollars into institutional review boards?

Mr. PUGLISI. I think every Federal agency that conducts human subjects research or supports human subjects research needs to find a way to provide better resources to support the IRB function, the VA included.

Ms. BROWN. Well, I am really troubled, and I have additional questions, Mr. Chairman, on the next round. Thank you.

Mr. EVERETT. Thank you. Our ranking member, Mr. Gutierrez, of the Health Subcommittee.

Mr. GUTIERREZ. Thank you. Thank you so much for being here this morning. What is pretty clear, 4,000, and you work on a system of trust, is that correct?

Mr. PUGLISI. That is essentially correct.

Mr. GUTIERREZ. So, did the West Los Angeles-Sepulveda situation break the trust?

Mr. PUGLISI. Yes, that is essentially why we withdrew our approval of the assurance. We felt that after many years of inter-

action with them, they were still failing to do very, very basic things correctly. Therefore, the trust agreement was broken.

Mr. GUTIERREZ. Could you just delineate for the committee what you consider the most egregious example?

Mr. PUGLISI. I can give you several examples. In 1998, the three institutional review boards involved held nine meetings during the months of May, June, and July. Seven of those nine meetings conducted business without a quorum, either by virtue of the number of members present or by virtue of the fact that the non-scientist member, who is required under the regulations, was not present. That is a very, very basic mistake. An IRB should not be conducting business without a quorum. If the institution doesn't recognize the importance of a quorum, we cannot have any trust in what they are doing in terms of protecting human subjects.

We had required, in our previous interactions with them, that they establish a Data and Safety Monitoring Board to oversee psychiatric research, particularly risky psychiatric research. We know that they had established such a body when we required it, but in 1998 we found no evidence that this body was operating. In fact, I was approached by a VA employee just yesterday who asked my advice regarding how they might reestablish the Data and Safety Monitoring Board. This, apparently, had fallen by the wayside.

Mr. ELLIS. Let me just interject, Tom, that is a very important point. The suggestion may be made that, because our staff resources are stretched thin or because we are dealing with information from the summer 1998, that our judgment on March 22, 1999 that the trust relationship could no longer stand is dated or out of date.

What Dr. Puglisi just said is that the requirement we imposed in 1994 to have an extra protection, a Data and Safety Monitoring Board was not in place through yesterday. We know because we got a call from an employee headed in the right direction, attempting to set up such a board, asking our advice on how to do it.

Mr. GUTIERREZ. Is there any other safeguard, other than your institution, for medical research at the VA?

Mr. PUGLISI. Research that is subject to Food and Drug Administration regulations.

Mr. GUTIERREZ. Food and Drug Administration—I guess Dr. Ellis—I mean, if you have 15 staff members, total, and you say you conduct three to four site visits a year, and you have 4,000 things going on at any time. It is not amazing that you begin an investigation in 1993, and in 1998 you finally reach a conclusion. Five years from the moment in which—to use your words, Dr. Ellis—you found a serious situation, a situation you thought merited your attention, and your oversight. You said that the facilities were across the street, and you had heard some other things that were going on, so you said—I don't want to misquote you or—in 1993, Dr. Ellis, you kind of said, "This merits our attention," and it wasn't till clearly 5 years later that any really definitive action was taken to take away the certification or their conducting their review. I think, Mr. Chairman, we need to look at—which both of the doctors have stated—and, that is, just how is it we have institutional review boards that really work? It is either that, or quadruple the staff over at OPRR, so they can get out and do more stuff, if it is

based on trust. And, what is the VA doing in terms of ensuring institutional review boards that are working adequately, not adequately, but excellently, which will stop these kinds of things from happening in the future? That is how I understand it, Dr. Puglisi, is that—?

Mr. PUGLISI. I think you are absolutely right. Certainly 5 years is too long for OPRR to take to reach this kind of action.

Mr. GUTIERREZ. So, if we do the institutional—but we have a problem because I just visited Hines Medical Center in West Chicago, Mr. Chairman, last week. I walked into the long term care facility, Mr. Chairman, and there were 12 patients, lunch was served to them. Obviously, they have no use of their hands. Lunch was served to them; I asked if there was inadequate staffing. They said, “No, we have enough staffing,” the director of the long term care facility there at Hines. I said “But, I have been here over 5 minutes, and nobody is being fed,” and she said “Oh, don’t worry, they will just reheat the food.” I felt like saying, “Well, maybe you should invite your family to dinner, tie their hands behind their backs, put a plate of food in front of them when they are hungry, and say, ‘Don’t worry about it, we will reheat it when I get around to it.’”

Mr. Chairman, we heard that the VA is going to cut 7,500 employees. This particular veteran—this is just one example—I don’t know how they are going to have anybody for institutional review boards, they don’t have people to feed the patients. Their goal, Mr. Chairman, is to reduce by 75 nurses and 25 doctors the facility in Hines, which is kind of the flagship out there in the Chicago region. If they are doing that there, I think this is part of a bigger problem we are going to have at the Veterans in terms of giving veterans good healthcare. Thank you very much, and thank you to both of the doctors for being here this morning.

Mr. EVERETT. Thank you for the gentleman’s comments. We actually have a case that came before this subcommittee where the nurses were eating the patients’ meals. We have actually had that.

Mr. GUTIERREZ. I believe it.

Mr. EVERETT. Dr. Snyder? Has Mr. Evans left? Dr. Snyder?

Mr. SNYDER. Thank you, Mr. Chairman. I want to ask if the process that you go through where you respond to complainants, I believe were your words, is that a formality? Can it be an anonymous complainant; can it be a newspaper report? What, of the hundred cases you have had, 34 in the last 9 years and the 67 pending, 101, how does it break down? Are they patients, family members, staff or third party outsiders?

Mr. PUGLISI. We receive complaints from all those sources that you named, and we do honor all of them.

Mr. SNYDER. Do you consider an anonymous phone call a formal complaint?

Mr. PUGLISI. We would talk to a person who made an anonymous phone call, but we would ask for something in writing, provided anonymously. We need something in writing to make sure we have an accurate understanding of the allegation. The largest source of information about non-compliance actually comes to us from institutional self reports. Usually that is in the context of an institution identifying a problem, and telling us that they have fixed it. But,

in terms of complaints that we actually investigate, we receive many complaints from family members, occasionally from subjects. We receive information from the media, and we receive information from the funding institutes that are conducting the research. They will, for instance, conduct a site visit, find a problem that seems to be related to human subject protection, and refer it to us. I would say about 30 percent of our complaints come from individual subjects or their family members. The rest come from the other sources you have named.

Mr. SNYDER. Of the 34 institutions in the last 9 years, are you satisfied that all of those have been corrected?

Mr. PUGLISI. We have a few institutions that are still under a restricted Assurance and are in the process of implementing corrective actions. But by and large, we are confident that human subjects are being protected adequately at those 34 institutions.

Mr. SNYDER. You made mention of the special responsibility towards people with schizophrenia, mental illness, I think, probably the real frail folks, the elderly, about the special responsibilities that the VA has to protect those patients. Is that responsibility any different than at a non-VA institution? Would you describe what those special responsibilities are with regard to a schizophrenia patient, a patient with mental illness?

Mr. PUGLISI. The regulations require that the IRB ensure special protections in any research where subjects may be vulnerable to coercion or undue influence. The regulations specifically name as vulnerable populations, pregnant women, children, prisoners, persons with mental disabilities. It is up to the IRB to institute appropriate protections for the specific population involved.

Mr. SNYDER. So, that can vary from institution to institution?

Mr. PUGLISI. It may vary from institution to institution. We recommend, for instance, that if there is any doubt about a subject being able to understand, that there be an independent process to assess that the person has the capacity to make an informed judgment. We recommend that there be independent monitors who can witness the informed consent process, and sometimes witness the actual research to make sure that the subject continues to understand and wants to participate. We recommend that there be waiting periods between the time that the subject is approached about participating in research until the subject actually provides consent, so that the perspective subject has time to think about it overnight, to ask other people, rather than to make a snap decision. All of these things are appropriate and should be implemented for vulnerable populations.

Mr. SNYDER. You brought up this problem of lack of resources for these institutional review boards. You are employed by NIH, is that correct?

Mr. PUGLISI. That is correct.

Mr. SNYDER. Why can't NIH contractually require some level of staffing, some level of funding, some percentage of any ongoing grant be applied to this process that you think is under funded? Is that not a requirement that could be contractually done with every grant NIH puts out? Has NIH identified a lack of resources as a problem? If they have, they get money. In fact, they have gotten

more money in the last couple of years than they ever had before. Why can't they solve some of these problems contractually?

Mr. ELLIS. There are two points to make. One is the Department's regulations, which are shared by HHS, the VA, and 15 other departments, explicitly require adequate staff, and meeting space for the Institutional Review Board. The second point is an institution's spending money on its Institutional Review Board is an allowable indirect cost when the institution receives Federal grant funds.

Mr. SNYDER. But, you all have been very clear you have not been satisfied with the level resources. It is one thing to say it is allowable; it is another to explicitly put in contracts that, I assume, go out every day, every week from NIH, and can be changed at any time that we have a problem here.

Mr. PUGLISI. You are absolutely correct.

Mr. SNYDER. Thank you, Mr. Chairman.

Mr. EVERETT. Mr. Doyle?

Mr. DOYLE. Mr. Chairman, I don't have any questions beyond those that have been asked already.

Mr. EVERETT. Mr. Buyer?

Mr. BUYER. Thank you, Mr. Chairman. I want to thank you for having this hearing, and for your conducting this oversight. I have just a couple of questions. At OPRR you have one physician and one attorney, is that correct?

Mr. PUGLISI. One physician and one attorney who conduct compliance oversight investigations, that is correct.

Mr. BUYER. Of about how many projects?

Mr. PUGLISI. We have no way of estimating how many projects are involved.

Mr. BUYER. I will estimate for you. Is it around 70,000?

Mr. PUGLISI. I would suspect that it is considerably larger than that.

Mr. BUYER. All right. Is it 100,000?

Mr. ELLIS. I would say you are in the right order of magnitude. It is not that we are ignorant of what we oversee, but our functional unit is the institution. So, we have got about 4,000 institutions with tens of thousands, perhaps 100,000 or more projects. Even the unit project is ambiguous. A single grant award can, sometimes, involve many protocols or many projects, a lot.

Mr. BUYER. Well, the one physician and one attorney must have an "S" on their chest to oversee up to 100,000 projects with a budget of \$300,000, I think, is woefully inadequate. This is an awful case. How come, Mr. Chairman, you always bring us the awful cases? You must be doing your job. I have a question about this—and, I think the right action was taken, I want you to know that. I think many of us may be concerned that we wish it had been taken a few years back.

Mr. PUGLISI. We share that concern.

Mr. BUYER. Explain this—the West LA obtained retroactive consents. Can you explain what a retroactive consent is? I know what informed consent is, but I don't know what retroactive consent is, nor do I understand its legality.

Mr. ELLIS. I think you are on to something. The only acceptable adjectival modifier for the noun "consent" is "informed." "Retro-

active," "surrogate," all those other adjectives just don't fit. I cannot disagree with your sentiment.

Mr. BUYER. So, you can't define that?

Mr. ELLIS. Retroactive consent is not an informed consent, given prospectively before the research interaction with the patient.

Mr. BUYER. What type of contact did OPRR have with the VA Washington headquarters regarding the problems at West LA?

Mr. PUGLISI. Essentially, we copied the VA on correspondence with the West Los Angeles VA. We copied the central office beginning in 1993.

Mr. BUYER. Any personal—

Mr. PUGLISI. We did not have extensive discussions with VA representatives.

Mr. BUYER (continuing). Any personal contacts out of the headquarters that would make you have a comfort level that they were informed that there was a concern?

Mr. PUGLISI. I believe we had mentioned it to the person who was the human subjects contact person for the VA at that time.

Mr. BUYER. What was that name?

Mr. PUGLISI. Mr. Ted Lorei. We did not engage in extensive discussions with the VA. We should have had better relationships with that agency.

Mr. BUYER. Do you know when—when a doctor goes beyond the consent, and based on either Government research or, perhaps, it is even a private research funding source, and he is gaining some intelligence and data, do you know—at West LA with its concern about the catheterization, do you know where this data was going, to the benefit of what institutions? Do you know that yet?

Mr. PUGLISI/ELLIS. No, sir.

Mr. BUYER. When will you be able to inform us of that?

Mr. PUGLISI. The cardiac research that has been in the media has not, up to now, been the subject of our investigation. We are going to be asking the VA for additional information. If any of that research is HHS-supported, we will have direct oversight over it. If the research is not HHS-supported, we will have no authority or jurisdiction.

Mr. BUYER. Then we would have to turn to the VA?

Mr. PUGLISI. That is correct.

Mr. ELLIS. Perhaps the Food and Drug Administration, I just want to add that.

Mr. BUYER. Is there a potential scenario whereby you could have a doctor, who is receiving multi source of funding for his research—NIH, VA, and perhaps, even a private source, would that be correct?

Mr. PUGLISI. That could happen.

Mr. BUYER. You could have some overlapping of three jurisdictions?

Mr. PUGLISI. Yes, there may be overlap. However, OPRR would have jurisdiction if there was any HHS support at all. So, even if research is only partially supported by HHS, OPRR has jurisdiction.

Mr. BUYER. All right. I thank you, gentlemen. I thank you for bringing it to everyone's attention. Again, I like you, wish it had

been earlier, and I also will take personal recognition of a woefully inadequate budget here based on your areas of responsibility.

Again, I thank you, Mr. Chairman, for bringing this up. This is definitely that cliché of putting the camel's nose under the tent. I am not so certain we are going to like what we see, nor what we smell. I yield back to the Chairman.

Mr. EVERETT. Thank the gentleman. Mr. Rodriguez?

Mr. RODRIGUEZ. I was just wondering in terms of from a liability perspective, have there been any lawsuits that have been filed or anything?

Mr. PUGLISI. I don't know of any lawsuits that have been filed relative to the VA West Los Angeles, but we wouldn't have that information.

Mr. RODRIGUEZ. So, even if there had been filed, you wouldn't know about it?

Mr. PUGLISI. That is correct. We would not, necessarily, know about it.

Mr. RODRIGUEZ. Even if it deals with a specific project that was funded, and—

Mr. PUGLISI. The only way we would find out about it would be for, either, the complainant, the person bringing the lawsuit to make it known to us, or for the institution involved to report it as a serious problem.

Mr. RODRIGUEZ. The institution itself?

Mr. PUGLISI. Yes.

Mr. RODRIGUEZ. Which most likely, they might not do that.

Mr. PUGLISI. You are certainly correct in that many institutions do not report to us all of the things they should report.

Mr. RODRIGUEZ. Let me ask you specifically, have you reviewed the VA's manual offering guidance about research with human subjects?

Mr. PUGLISI. Yes, we have. We have looked at the manual that was submitted to us in November of 1998.

Mr. RODRIGUEZ. And, do you see any—from a legal perspective in terms of liability?

Mr. PUGLISI. I am not an attorney, and liability is not something that our office handles. So, I don't think I should comment on the liability aspects of it.

We were disappointed to find some continuing problems with the procedures manual that was given to us in November of last year, particularly related to the statement that the VA had not yet finalized their plans for a Data and Safety Monitoring Board some 4 years after we had required one.

Mr. RODRIGUEZ. I am sorry, repeat that again?

Mr. PUGLISI. In 1994, we required the VA West Los Angeles to set up a special Data and Safety Monitoring Board for psychiatric research. The manual that they gave to us in November of last year stated explicitly that they were in the process of setting up such a Data and Safety Monitoring Committee, but the procedures for the committee had not yet been finalized. This was some 4 years after we required them to do so.

Mr. RODRIGUEZ. So, even after 4 years—do you know if that has taken place now?

Mr. PUGLISI. I spoke with a VA employee yesterday who asked me questions about how they might go about reestablishing that committee. So, as of yesterday, it was not operational.

Mr. RODRIGUEZ. So, there is no indication, at least, by practice that they are even having intentions of doing that, then, except giving you a verbal commitment?

Mr. PUGLISI. A verbal commitment is what we have at this point.

Mr. RODRIGUEZ. No actual in practice after how many years now?

Mr. PUGLISI. We had indications that they had set up such a board originally because they reported to us that they had. My suspicion is that it fell by the wayside at some point.

Mr. RODRIGUEZ. Or that it was never there, was just in paper?

Mr. PUGLISI. That is possible.

Mr. RODRIGUEZ. No further questions.

Mr. EVERETT. Thank you. I see all members have had an opportunity. Let me ask you, Doctor, OPRR in its testimony concludes that VA should set its aim well beyond minimal compliance with regulatory standards. Are you saying that the VA does not now do that?

Mr. PUGLISI. Well, we certainly believe that at West Los Angeles the procedures that we saw failed to meet even minimum standards.

Mr. ELLIS. I will give you an example. The rule says that there has got to be a non-scientist present in order for the Institution Review Board to conduct business. It says "at least one" non-scientist, so if you aim for minimal compliance, you put one non-scientist on your IRB. So, that individual doesn't show up for a meeting, and you don't have a meeting that day. If you aim beyond minimal compliance, you put two non-scientists on, and then it is all right if one of them doesn't show up, you still have a quorum. So, we are talking about very specific items of aiming beyond the minimum to enable the system to work.

Mr. PUGLISI. Let me give you another example at West Los Angeles. It took the VA West Los Angeles about 2 weeks to come up with a list of HHS-supported research at their facility. Two weeks—this list is something they should be able to generate in 5 minutes. How can an institution establish any accountability if it doesn't even know what research it is conducting. The VA has asked for an extension of 3 months to examine their portfolio of research and re-review that research. Apparently, the VA needs this amount of time to make sure that the research has received an adequate review. This indicates to me that there were very, very serious problems at West LA, and that the action taken by OPRR was the correct action.

Mr. EVERETT. Finally, doctor, you have said that you are not an attorney. But, as a doctor in charge of heading up OPRR, let me ask you as a doctor. The case in West Los Angeles, the cardiac case, as a doctor, would you say that that constitutes criminal assault, or certainly, patient abuse?

Mr. PUGLISI. I am not a physician, and I don't have all the facts, so I don't think I should comment on it.

Mr. EVERETT. The gentle lady have an additional question?

Ms. BROWN. Yes, sir. I would like to know more about challenge research, in which additional stress is put on the patient. We have

seen research in which mental health or chronic patients are not only taken off medications that has been helpful to them, but are subjected to worsening or deterioration of their condition by the use of other drugs. This sounds really grim to me, but I am not a scientist. Is challenge research good for the patient?

Mr. PUGLISI. I don't think anyone would argue that patients or subjects receive benefit from challenge studies. Challenge studies, as I understand them, are conducted purely for research purposes. They are an attempt to bring about or mimic certain symptoms so they can be studied scientifically. There is no benefit to individual subjects of challenge studies.

Ms. BROWN. Does the patient know that they are participating in research that may be good for mankind but could worsen their condition?

Mr. PUGLISI. Subjects should have that information, should be told that. We have certainly found instances where we were not convinced that the informed consent process adequately conveyed that information.

Ms. BROWN. I am convinced that OPRR needs more funding and more staffing. This is not meant to be a criticism, but feedback in effect, really. Is trust an adequate basis—if we have more investigators? I am concerned about this trust.

Mr. PUGLISI. I think what we need is a system that has well-monitored trust relationships. And, I thank you for your observation.

Ms. BROWN. Thank you. That is it for me, Mr. Chairman.

Mr. EVERETT. Thank you. Dr. Snyder?

Mr. SNYDER. Thank you, Mr. Chairman. Just for clarification, would you outline your staff size again since that is some interest? Your total staff is how many?

Mr. ELLIS. The office, as a whole, has about 32 people. We oversee laboratory animal welfare, and human subjects in research. We have about 15 or 17 people that are dedicated to human subject protection, and of those, two professionals are full-time investigators, one physician and one attorney.

Mr. SNYDER. That is not augmented by any contractual staff?

Mr. ELLIS. We do have three part-time contractors that help us with investigations, each less than half time. That aid ebbs and flows as funds permit.

Mr. SNYDER. Your 15–17 is about the size of the average congressional office, and they only have to keep up with one member, not 4,000 institutions.

I want to ask—you made reference to the joint appointments, which are very common, joint appointments between VA hospitals and medical schools. Has that process or that fact of joint appointments, which I assume, then, means dual oversight—you have both the medical school, and the VA center partnering in a grant, and that they both have reporting responsibilities, does that help or hurt? Does that complicate it, and make it less likely to pick up problems? Or, because you have a dual oversight, is that more likely to turn up problems?

Mr. ELLIS. I am going to answer that question with a specific about this case, which would be most meaningful. One might think

that dual oversight would give two layers of protection. If one layer failed, we would still be all right.

In this case, for some HHS-supported research, there would be an expectation that both the awardee institution, UCLA, for example, and the VA West Los Angeles Institutional Review Boards would be reviewing the research. The example is the award goes to UCLA, but the performance site is across the street at the VA Medical Center. We would have an expectation of review by IRBs at both places. What we find today is that, apparently, some number of HHS awards to UCLA where the performance site was the VA, were not reviewed by the UCLA IRB, and we have serious questions about the review that did take place at the VA. So, rather than having an extra layer of protection from two overlapping reviews, we find, maybe—I don't know what to call it—a tragedy of the commons, where both parties thought the other might be doing it.

Mr. SNYDER. If more than one person is responsible, no one is responsible.

Mr. ELLIS. Thank you, sir.

Mr. SNYDER. Now, that would seem to me to be another thing that you all could take care of contractually, though, in those kinds of—with some special language related to those dual kinds of grant recipients.

Of your 34 closed cases, and your 67 pending cases, how would you rank, without commenting on any of the 67 pending, how does this case, the West LA case, how does it rank in severity compared with the other 100 cases?

Mr. ELLIS. With a large number of cases, and limited resources, we do a triage, actually, in the office. We say what have we got to work on today? We are juggling 67 cases, which one is going to land on someone's desk this morning?

Our highest priority is always a case where an individual subject could be at risk at this moment. Subjects are subjects. In contrast, we have what I will call old cases or cold cases where it appears that there was institutional failing in the past. They don't seem so serious to suspect that individual subjects may be at risk at present. Then, there are a variety of cases in between.

This case, the West LA VA was not as serious as some because we didn't have an identifiable individual hurt. It was the enduring nature of the non-responsiveness that precipitated our action.

Mr. SNYDER. Now, is it fair to say—and don't let me put words in your mouth—were you concerned that that enduring non-responsiveness at some point might put patients at risk or not?

Mr. PUGLISI. Certainly. Certainly, we had that concern. If the process is not as it should be, there is essentially no protection. Where there is no protection, people can get hurt.

Mr. SNYDER. And, my last question is, there was an earlier reference to firing of employees, and I don't know if I heard a response to that. But, without going into specifics with regard to the pending case, of the 34 closed cases over the last 9 years, how many of those resulted in some type of termination of employment on the part of any of the folks who committed the infractions?

Mr. ELLIS. That is a very difficult question for our office to answer but we, certainly, as careful observers of the institution, note

turnover in personnel in the wake of our actions from time to time. Turnover of personnel at the institution, I should say.

Mr. SNYDER. So, that has—

Mr. ELLIS. That has happened, yes.

Mr. SNYDER. Thank you, Mr. Chairman.

Mr. EVERETT. Thank you. Mr. Doyle? Mr. Rodriguez and Mr. Buyer, I apologize. I overlooked Mr. Rodriguez, my good friend, earlier. Mr. Buyer?

Mr. BUYER. I just want to follow up on Dr. Snyder's questions because I think he is following a very good path. If at UCLA and at West LA, if they have this project Assurance, and it also comes under the auspices of the HHS review board, and UCLA corrects their problem in 1992, how come VA couldn't get theirs corrected?

Mr. PUGLISI. Well, the corrections at UCLA began in 1992 but took considerably longer to implement fully. I believe we finally closed our case with UCLA in 1997. So, we had identified serious systemic protections at UCLA, as well, and worked with them for a number of years to create a system in which we had confidence. It involved, on UCLA's part, a very large influx of resources, a very large addition of staff, and a great deal of training of their investigators and researchers.

Mr. BUYER. If you have got this Multiple Project Assurance, and you are working hard, and it has taken years with UCLA, and you have your other partner in this, how come it didn't just marry up to a dual correction?

Mr. ELLIS. These are separate institutions. There is no question, they are right across the street; there are some joint appointments; there is some overlap. At UCLA we identified, through the mid-1990's a culture of non-compliance with Federal human subject regulations, and so labeled it.

Mr. BUYER. But, your testimony to us is that within your jurisdiction, all you can do is cc the VA, is that what you are telling us?

Mr. PUGLISI. No, I am saying that we should—in retrospect, we should have had closer contact with VA Central Office, and we should have made them aware of the serious concerns that we had. I don't think we did a sufficient job in that regard.

Mr. BUYER. All right. I think the nobility of our cause here to the protection of a vulnerable population in research is what everyone wants. Now, I am going to ask for your professional judgment, along with your personal opinion so we will know what the size of this concern is—whether this is an isolated incident based on this culture that you just talked about in West LA or does it go into the Philadelphia—the opening of these new investigations in Cincinnati, Philadelphia, and Tampa, is this based on your professional judgment, and your personal opinion, are these isolated or is this a cultural concern that goes beyond these isolated incidents?

Mr. PUGLISI. You mean a cultural concern within the VA, or within the scientific community? I think there are some disciplines within the scientific community that have less regard for or awareness of human subject protections.

I think that, to the extent that institutions fail to recognize that they have a problem until that problem hits the front page of the *New York Times* or the *LA Times*, Institutional Review Boards and

the human subject protection system are likely to be under funded because administrators usually don't see it as their most pressing concern. To the extent that VA Medical Centers are under funded, I think it is safe to assume that the human subject protection system is also under funded. Very few institutions fund their IRB, their human subject protection process first. Most of the time, human subject protections are at the end of the pecking order, not at the beginning.

Mr. BUYER. I want to pick up off something that the ranking member brought up about this serving of the greater good. Is it within now—help me understand part of the cultural justifications within the research community. Do they, somehow, sort of justify that they can go beyond the consent because they are serving the greater good? How is it they justify such actions?

Mr. ELLIS. I think there is a failure to distinguish between treating a patient, and pursuing new knowledge for the greater good. Patients need treatment; that is healthcare. Ordinarily, people don't need to be research subjects. They may wish to be for a variety of reasons, and that is fine. People may wish to take risks, that's an option on their part, and they have to know what they are getting into. It is the failure to distinguish treatment from research that is at the basis of some physician researchers going wrong here.

Mr. BUYER. Thank you. I yield back.

Mr. EVERETT. Thank you. Mr. Rodriguez?

Mr. RODRIGUEZ. Thank you, Mr. Chairman. Regarding NIH, and I realize we are talking about the VA. But, I also have had some concerns with NIH, and I just sent a letter about the fact that, aside from some of its ways of funding, and I recognize there is a process to try to allow so it is research oriented and it is research guided. But, there have been some concerns, at least I have some concerns that I have already indicated to Secretary Shalala regarding NIH, and that is its lack of connectiveness to the community, and there is a lack of impact from the community as to where they should be doing research or in what areas. I was wondering if you want to make any comments in that area because I know that I have had some problems from that perspective with NIH? I have had my problems with VA, but I am referring now to NIH.

Mr. ELLIS. I think it is a very timely comment. I know the NIH director is thinking along the same lines, and by coincidence today in Bethesda, he is chairing the first meeting of his newly appointed Council of Public Representatives. So, this is a group that was just named this week, it met yesterday for orientation, meeting in full session today. So, these are the type of individuals you describe, call them ordinary citizens, they are each, actually, extraordinary individuals. But, this is a new group to meet twice a year to advise the NIH Director on just the sort of issues you are raising.

Mr. RODRIGUEZ. I would ask that you send me a copy of those individuals that are participating in that process, if you can?

Mr. ELLIS. I would be pleased to do it.

Mr. RODRIGUEZ. And, I was wondering if you have any obligations from your role to make any recommendations regarding NIH?

Mr. ELLIS. I don't hold—

Mr. RODRIGUEZ. Holding NIH responsible and accountable for what it funds or doesn't fund, or what it does and doesn't do?

Mr. ELLIS. Well, as you know, our office is part of NIH. We are not, however, involved in identifying specific subject matter to be supported for research. It is just beyond our office's purview.

Mr. RODRIGUEZ. Is there anything within NIH that assesses that?

Mr. ELLIS. NIH has a very well developed system of peer review, scientific review to select among the many opportunities for research in biomedicine and behavior.

I am just suggesting your question may be misdirected to our office, that is all.

Mr. PUGLISI. I think, relative to what our office does, we have encouraged institutions to place community members on their institutional review boards in numbers far greater than the minimal regulatory requirement. We believe that it is very, very important for representatives of the community in which research is going to be conducted to take a role in evaluating the propriety of that research. Some institutions have followed our guidance, other institutions have not. Some members of the scientific community seem to be uncomfortable with opening up the IRB process to greater numbers of community members. Other members of the scientific community embrace it.

Mr. ELLIS. We have addressed this in additional ways as well. I can tell you we met with the American Legion this week, and we had a very constructive meeting. We said, "Look, the Legion has members in all 50 States and territories around the country; these are potential institutional review board members." I think that that is the kind of involvement in this oversight process that we want to foster.

Mr. RODRIGUEZ. But, as you well indicated, when you have too many, you might have none.

Mr. ELLIS. We need to increase, incrementally, the lay involvement, the community involvement in the process of oversight of research. The regulations describe minimal participation. So, that is the only tool we have. There has got to be one non-affiliated member on the Institutional Review Board, meaning not affiliated with the institution. There has got to be one non-scientist. That can be the same individual, actually, the non-scientist who is not affiliated. That is the minimum requirement. We like to see institutions go beyond that.

Mr. EVERETT. Gentlemen, I want to thank you. I couldn't help but pick up on your comment of the culture of non-compliance. This committee has been faced with a cultural problem in the VA for a number of years to include sexual harassment, the mismanagement of millions of dollars, attempted coverup, in my opinion, of 40 deaths at Columbia, Missouri hospital. As a matter of fact, I could take more time than we have got to continue this. We made it well known to the VA that we feel like that culture that exists in the VA must change or VA won't survive it.

Thank you very much for your testimony today.

Mr. PUGLISI/ELLIS. Thank you, Mr. Chairman.

Mr. EVERETT. I would like to call up Panel II. Dean Norman, Acting Chief of Staff, West Los Angeles VA Medical Center; Stephen

Pandol, Former Director of Research and Development, West Los Angeles VA Medical Center; Ken Clark, Chief Network Officer at the Department of Veterans Affairs, and the Former Director of the West Los Angeles VA Medical Center; and, Ron Norby, Clinical Manager and Deputy Network Director of VISN 22.

Would you all rise, please?

[Witnesses sworn.]

Mr. EVERETT. Thank you very much. Please be seated.

Dr. Pandol, I understand you are the only one who will make a statement today. If you will, please proceed. I am going to ask you, please, limit your statement to 5 minutes. Your complete statement will be made a part of the record. The members have already read it. Unfortunately, we just really can't take more than 5 minutes on these statements. If you will limit to 5 minutes, and please proceed.

TESTIMONY OF STEPHEN PANDOL, FORMER DIRECTOR, RESEARCH AND DEVELOPMENT, WEST LOS ANGELES VA MEDICAL CENTER, DEPARTMENT OF VETERANS AFFAIRS; ACCOMPANIED BY DEAN NORMAN, ACTING CHIEF OF STAFF, WEST LOS ANGELES VA MEDICAL CENTER, DEPARTMENT OF VETERANS AFFAIRS; KENNETH CLARK, CHIEF NETWORK OFFICER AND FORMER DIRECTOR, WEST LOS ANGELES VA MEDICAL CENTER, DEPARTMENT OF VETERANS AFFAIRS, AND RONALD NORBY, CLINICAL MANAGER AND DEPUTY NETWORK DIRECTOR, VETERANS INTEGRATED SERVICE NETWORK 22

TESTIMONY OF STEPHEN PANDOL

Dr. PANDOL. Thank you, Mr. Chairman.

Mr. EVERETT. Would you have your attorney identify himself for the record, please?

Mr. KRANE. My name is David Krane of the law firm of Krane, Lowell and Ingram.

Mr. EVERETT. Thank you. Please proceed.

Dr. PANDOL. Thank you, Mr. Chairman, ladies and gentlemen. My name is Stephen Pandol, M.D. There have been innumerable allegations made toward the research administration of the West Los Angeles VA Medical Center. My purpose today is to provide important factual information and to submit to you suggestions that may be useful in improving the performance and safety of our human research in the Department of Veterans Affairs.

The concern that the members of your subcommittee have expressed about the issue of safety and human research at our facility is exactly the concern I had 3 years ago when I took my position. Within days of arriving, I was informed of problems in cardiology and cardiology human research. There had been an investigation of the problems, but some individuals came to me and told me that the investigation was a white wash. I stopped the research of three medical investigators, and demanded of the chief of staff that a more exhaustive investigation of the problems take place.

The ensuing board of investigation lasted approximately 6 months. The Chief of Staff requested that I not be a member. As a result of that investigation and because of other observations, re-

search administration took a hard look at the issues surrounding safety and oversight of human research projects. The measures we instituted have had significant impact on improving safety and oversight. I firmly believe that these activities serve as a model for ensuring safety of human research. I urge you to ask questions about what we have done.

Although we made substantial improvements in human research oversight, our efforts were thwarted by severe financial problems we inherited, and extreme difficulty in obtaining resources to provide adequate staffing. The VA research appropriation only provides research administrative support funds for grants funded by the VA. Only 25 percent of our research portfolio was VA-funded. About one-half of our research administrative costs were related to non-VA projects which included those from our own non-profit research corporation, UCLA, and the National Institute of Drug Abuse, nor NIDA. Administrative services for these projects were provided without compensation.

Our research portfolio is one of the largest in the Nation, so the ramifications of this dilemma were profound. My research staff began to develop creative ways to reimburse for our services. Basically, we were using VA research funds to provide services for other organizations, agencies and companies. Even attempts to rectify this situation with our own non-profit research corporation with its corporate contracts were met with severe obstacles from VA management and our legal department. We received no support from UCLA, and the National Institute of Drug Abuse, or NIDA, argued vehemently over issues surrounding administrative support. NIDA, I might add, even strongly argued against allowing our research department oversight function over major a cocaine project that was in place on our campus. I urge you to ask questions about this.

Finally, I had no success in urging management to use resources provided in the medical care appropriation for research support to address the desperate needs of research. I estimated that annually our medical center used only about one half of the \$20 million in this category that it receives to support research. Our research facilities are the worst in the Nation.

The issue that has most recently focused your attention on safety and oversight in human research revolves around the shut-down of research at West LA. Within 24 hours of our notification of the action, the research staff provided a point-by-point response to all issues delineated by OPRR. Our report indicated that the action to rescind the multiple project assurance status was based on misinterpreted and out of date information. I am not sure that this report was ever brought forward by management.

As delineated in my written statement, OPRR did not communicate with West LA for over 2 years. Neither my superiors, my predecessors, nor VA headquarters ever informed me of the OPRR restriction. Once we learned of the restriction, we attempted to address all outstanding issues, and provide materials to OPRR. OPRR made the decision to rescind our MPA without a site visit or without any telephone calls or dialogue with the research department.

Lessons learned from the VA Medical Center should, hopefully, result in facilitating the dedication of effort and resources to pro-

mote the development of a safer and more enlightened and productive system of human research. The conduct of action to halt all research at the VA Medical Center, and to rescind the MPA status only served to punish one organization whose difficulties are merely a reflection of those that permeate our IRBs and research departments nationally.

George Grob, in his report entitled, "Institution Review Boards, a Time for Reform," states that the oversight process should focus less on mere compliance matters, and more on performance issues. Be assured we do care deeply about veterans and public health, and we hope it becomes apparent that we did markedly improve human research safety at West LA. Furthermore, as several of you have indicated, the research we do provides significant advances in health to our veterans and our Nation. Thank you.

[The prepared statement of Dr. Pandol appears on p. 105.]

Mr. EVERETT. Thank you. I am informed the rest of the panel will rely on the official VA statement, is that correct?

Dr. PANDOL. Yes.

Mr. EVERETT. Dr. Pandol, I know there is a lot at stake for you today, but let me get a couple of things straight.

You seem to believe that the suspension of research at West VA was not justified. But, you also say that you were not getting the support you needed from your supervisors, is that correct?

Dr. PANDOL. Yes, to be really clear, there are some issues with the OPRR report that I think are incorrect, and that they need dialogue and discussion. That hasn't been done. But, you are right, the support was meager.

Mr. EVERETT. And, those issues of OPRR are pointed out in your statement, which I have read.

Doctor, you have been reassigned from your duties as Director of Research at West LA. I am not aware that anyone else above you has been reassigned. Do you believe you are being made a scapegoat?

Dr. PANDOL. I think it is a possibility. I think, as we are learning today, and I have tried to explain—this is an extremely complex problem with a lot of issues involved. I am an easy target.

Mr. EVERETT. Who is in the chain of command above you?

Dr. PANDOL. My supervisor was Dr. Dean Norman, Chief of Staff.

Mr. EVERETT. Has anything happened to Dr.——

Dr. PANDOL. I don't know. He would have to answer that.

Mr. EVERETT. Is it correct that the National Association of Veterans' Research and Education Foundation offered you any kind of services and administrative support for the West VA research service, but not actual funding, and you did decline the offer?

Dr. PANDOL. That is not true.

As I alluded to in my talk, and also in my prepared testimony, we had an argument over approximately 2 years on funding for one aspect of human research oversight. That was the oversight that was required for the contracts and grants that went to our research non-profit corporation. Over 2 years, we received gifts of approximately \$200,000 each year. I must say that the money used to come at the end of the year or into the following year, and it made it extremely difficult for us to have stable staffing. So, at the end of 1998, we made an arrangement so that we could have stable

staffing. What we did is we came to an agreement with the non-profit research corporation, so that there would be payment in kind by the non-profit corporation in the way of having employees of the non-profit research corporation help with staffing in IRB and oversight functioning. That started in approximately October, and was being implemented through the later part of the year into the first part of the following year.

However, what was so disappointing to me is that, in a meeting in January of 1999 after I had thought this was completely set and we could have stable funding from at least this one component of our portfolio, the Chief of Staff argued with me at a board meeting that the non-profit board had no responsibility to continue that funding, and that decisions should be made on a case-by-case basis. I argued so hard that night—I actually ended up in the hospital the next day. It was very frustrating.

Mr. EVERETT. Let me switch subjects just for a moment, and ask you, Dr. Pandol, what do you know about the case of a doctor who did research without consent, Dr. Phillip Sager? Why didn't you report it, and did anyone ever tell you not to report it?

Dr. PANDOL. I became aware of that when I started my position. There had been an investigation——

Mr. EVERETT. Before or after the occurrence?

Dr. PANDOL. After the occurrence was before I started. Is that what

Mr. EVERETT. Yes, that is what I am asking.

Dr. PANDOL. The occurrence was before I started. There had been an investigation in the organization, I understood, and people in the organization came to me, two individuals in the organization came to me. They said they had heard about this investigation, and they said, "There is something wrong, there must be a white wash, there is nothing significantly happening here. Could you look into it?" So, what I did is I went to the Chief of Staff, and I said, "I am hearing rumors that there is a problem in cardiology and cardiology research. I don't know all the facts. There are a lot of different allegations. I am not sure what is wrong. I did hear that there was an investigation, but it looks to me like there has to be a more extensive or exhaustive investigation of this problem." He, in turn, set up a board of investigation to evaluate the issues.

Mr. EVERETT. Doctor, do you know what discipline the doctor—and, why didn't you report it, I am sorry?

Dr. PANDOL. I did report it. I reported it to my supervisor.

Mr. EVERETT. Okay. Did you know what discipline the doctor was supposed to receive, and whether it was actually imposed?

Dr. PANDOL. Could you repeat that once more?

Mr. EVERETT. Dr. Sager, do you know what discipline he received for this, and if that discipline was actually imposed on him?

Dr. PANDOL. I do not know that. That is not in my authority. That was in the authority of the Chief of Staff.

Mr. EVERETT. Why do you seem to know so little about this? Were you kept in the dark about some things or——

Dr. PANDOL. I was not told about the——what do you call it—the——

Mr. EVERETT. Cardiac procedure?

Dr. PANDOL. No, I learned about all that. I know about the board of investigation. But the discipline I was not involved in. That was, apparently, a private discipline matter between the Chief of Staff and the individual. I have no authority or right to know about that.

Mr. EVERETT. I see my yellow light is on. But, I have additional questions, and we will have a second round. Let us see, Dr. Snyder?

Mr. SNYDER. Just one specific question. It is really unrelated to the issue today—I guess related indirectly. But, the quality of research buildings? You know, I am a big believer in research being done at the VA hospitals. I think patients benefit from it; I think a lot of them like it; I think they like to be at the cutting edge of things, if they understand what is going on. But, good research is going to be difficult to do in poor quality buildings. You may have a comment on that?

Dr. PANDOL. That is a severe problem at the West Los Angeles campus. The buildings the research is done in right now were approximately built in 1930, and they rehabed a hospital and renovated hospital wards. There had been proposals going to the Department, as early as I can find in 1984, saying it was an unsafe and inefficient environment. The Department, at that time, did not act on it. We submitted, out of my office, a request to our facilities department in 1998, and I have not gotten any feedback whether there was any action taken on that proposal.

Mr. SNYDER. Do you have a comment on it?

Dr. NORMAN. A similar comment that the buildings are very old and constantly falling apart, and require a lot of money to maintain them from year to year.

Mr. SNYDER. I don't have any further questions, Mr. Chairman. Thank you.

Mr. EVERETT. Thank you. Mr. Doyle.

Mr. DOYLE. Thank you, Mr. Chairman.

I want to get this in perspective. I want to talk about this Dr. Sager investigation. You are saying that the incident that has been revealed took place before your tenure. Then, when you got there, you looked into this situation further. Tell me about the board of inquiry that took place? The allegations are that a patient twice refused, that he did not want to be a participant in this research. And, Sager just went ahead, kept him on the table an additional 45 minutes when this patient expressly said he did not want to be part of a research project.

Dr. PANDOL. Right, I think it is best that Dr. Norman answer that question.

Mr. DOYLE. And, then, from that, there was a board of inquiry?

Dr. NORMAN. Actually, what happened was that we heard some rumors that there were problems in cardiology. There had been fighting between the staff members when I started, which was about 1993, as Chief of Staff for the West LA Facility, and some of the members were complaining about—particularly Dr. Sager—and, Dr. Sager was complaining about other members, as well. On that basis, a Dean Emeritus from UCLA, Dr. Mellenkoff, was assigned by the Chief of Medicine to review issues in cardiology and some of the allegations, particularly relating to Dr. Sager. In his review, he found that there was a sloppiness in the research being

done by Dr. Sager, but no actual patient abuse or scientific misconduct.

However, Dr. Pandol and, actually, several other people had come to me and stated that they felt that that was, in fact, a white wash. It was not a careful look at what was going on in cardiology. Therefore, I appointed a board of investigation. The board of investigation reviewed allegations made, specifically, by one or two people in the Cardiology Department. In one of those allegations, there was a patient, who was undergoing a clinical procedure, and had twice refused before, to give his consent for the research procedure. Now, he was undergoing a clinical procedure. This was a procedure presumably to benefit his clinical condition, and during the procedure, Dr. Sager did a modified research project, something called a mapping procedure, which I am just learning now is where you put the catheter in different parts of the heart, and map the abnormal areas. Now, the patient had not consented to that procedure, so that technically, Dr. Sager was doing research without his consent. It did prolong the procedure, and the data was used for scientific purposes. So, very clearly, that was not having informed consent, and violated the scientific integrity, and certainly violated the trust of the patient.

Mr. DOYLE. So then, there is no dispute that this research was done on this patient without his consent. In fact, he had said he did not want to do this. Now, this board of inquiry, who sits on this board? And, does anybody on this board of inquiry that looked into this case do any co-research with Dr. Sager? Is there any affiliation with him; is it an impartial board of inquiry?

Dr. NORMAN. At the time, I felt it was a very impartial board of inquiry. Although it didn't have Dr. Pandol—I don't remember why he was not on the board—we would usually in these cases like to have the Associate Chief of Staff for research on the board. It was, perhaps, because he was brand new, but we did have his administrative officer, Kathleen Barrett, who was on the board. Unfortunately—the board went several months—some time during that period of time, she took another job. So, she did drop off the board. But, certainly, the report of the board was made familiar to Dr. Pandol, and he actually monitored Dr. Sager for, actually, over a year after the board. I can go specifically on who was on the board at the time, if you like? But, what we found—I think a couple or 3 years later—I learned that there was an issue with Dr. Sager's name and one of the board members appearing on a publication. Mr. Norby knows more of the details about that than I do. Maybe you can answer that?

Mr. NORBY. Yes, I would be happy to. One of the members of the board was a representative from our headquarters, Dr. Pamela Steele. Dr. Steele was involved in some research involving implantable pacemakers, which was done at various sites throughout the country. Her involvement was at the Washington, D.C. VA Medical Center. She was working with a team of scientists there, studying the effects of implantable pacemakers. Dr. Sager was working with another team on the other side of the country doing a similar kind of study. It was an abstract that was developed, actually written by one of the investigators at the Washington, D.C. VA Medical Center, and that abstract listed the names of Dr. Sager

and Dr. Steele—both in that abstract. So, that is really the only association. She was not involved, in any way, in doing research with him.

Mr. DOYLE. What ultimately happened to Dr. Sager as a result of all these investigations and this board of inquiry.

Dr. NORMAN. Initially, when we learned of the allegations and the substantiated allegations, certainly everyone was outraged. I personally felt that we should strongly consider removing Dr. Sager.

However, the board recommended a measured response for many reasons. One was that Dr. Sager appeared to be, not a malevolent individual, but someone who, certainly, was sloppy; someone who didn't pay particular care to getting the informed consent himself. He had his other people, his fellows, et cetera, doing that. No patient was actually harmed by anything he did. He also was relatively young. This was the first time that he had committed any errors.

I did discuss this issue with multiple people, including Mr. Clark, CEO, Chief of Medicine, Dean Emeritus at UCLA, and the hospital ethicist. And, it was clear based also on the board report, that firing him would not be the measured response. So, we ended up suspending him, and having him go through a monitoring period with Dr. Pandol monitoring his research.

During that period of time, he behaved in an exemplary fashion; we received no complaints about Dr. Sager, and Dr. Pandol assured me that things were going well with his research. So, he was monitored very carefully; he did well during that monitoring period. But the idea of the suspension; you have to understand, a suspension is not a minor disciplinary action for a physician. It is one step away from being removed. That suspension, although I think Dr. Sager tried to keep it quiet, was well known in the scientific community. Dr. Sager complained to me that, at national meetings, people were bringing that up.

So, his reputation was certainly tarnished, and he did suffer by it. What we found in the investigation of the suspension in the last few weeks was that, in fact, he only served 7 out of the 10 days of the suspension. So, that is being remedied. But, the idea of the suspension was that—and I told him this—he was hanging by a thread, and that any other behavioral problems, any other difficulties in his research, any other problems whatsoever in cardiology related to him, that he would be leaving the institution. And, he understood that.

Mr. DOYLE. We are going to have a second round of questions. Thank you, Mr. Chairman.

Mr. EVERETT. Absolutely. We have 10 minutes. Would the gentle lady like to go vote?

At this point, we will recess until the members have returned.
[Recess.]

Mr. EVERETT. The hearing will resume. I remind the panel that you are still under oath, and we will have additional questions, probably, for the record, from some of our members.

Dr. Norman, how long have you been Chief of Staff at West LA?

Dr. NORMAN. I have been the Chief of Staff from about 1993, and when we merged with the Southern California System of Clinics re-

cently, I became the Acting Chief of Staff for the Greater Los Angeles Health Care System.

Mr. EVERETT. What was your role and responsibility for research at the Medical Center? Who was in charge, it wasn't you, is that correct?

Dr. NORMAN. Well, technically, the ACOS for Research was in charge of research, but that person reported to me, even in my capacity as the Acting Chief of Staff for the Greater Los Angeles Health Care System.

Mr. EVERETT. Dr. Norman, did anyone ever tell these four veterans who didn't consent to the research what happened to them?

Dr. NORMAN. Yes, specifically, they were contacted by telephone, those that we could reach. And, I sent letters, also, to them.

Mr. EVERETT. Was that—as far as the—I am trying to make up my mind which way to go here. Excuse me, Dr. Norman.

Let me ask you just a second about the retroactive consent that was obtained from two veterans for research already performed. Do you think that is a good operating procedure?

Dr. NORMAN. No, it is not informed consent.

Mr. EVERETT. Who attempted—who did that?

Dr. NORMAN. This was the recommendation of the board of investigation in the case, that those veterans that had undergone research procedures without informed consent, that they still afterwards be consented. That is not the same as informed consent. I think it was an attempt in the recommendation by the board to make sure that the veterans understood exactly what happened to them.

Mr. EVERETT. In other words, that was the reason it was done, and that was the only reason it was done. It wasn't somebody down there trying to cover up something?

Dr. NORMAN. Well, yes. Let me assure all the people here there was no attempt, whatsoever, to cover up this up. In fact, we did have a representative from headquarters who served on the board. Second of all, there were one or two members of the Cardiology Department who were very unhappy that Dr. Sager was not fired. They insisted they were going to go to the newspapers and tell everybody they could about it. I assumed that they would do so, and they did. I thought, at the time, that the board of investigation did a very thorough job. They made good recommendations, and the recommendations were carried out. There was no attempt by myself or anyone to cover up their findings.

Mr. EVERETT. The suspension that you have described as being severe, was that a ten day suspension or ten week suspension?

Dr. NORMAN. It was a ten day suspension.

Mr. EVERETT. With pay?

Dr. NORMAN. Without pay.

Mr. EVERETT. Without pay. Was it ever imposed?

Dr. NORMAN. In our recent investigation, he served seven of those 10 days without pay, and we are—either has or about to give him the other 3 days suspension.

Mr. EVERETT. Did you discuss with the VA counsel whether any criminal acts, such as assault and battery, might have been committed by, willfully, conducting research on patients without consent?

Dr. NORMAN. Yes, I did.

Mr. EVERETT. Were you aware that it is a violation of California law with a maximum of \$10,000 fine, and a year in jail?

Dr. NORMAN. No, I wasn't aware of that until just recently.

Mr. EVERETT. Would you explain to me the logic behind—the board or whoever made that decision—the logic behind declaring that this was not battery or patient abuse or criminal assault?

Dr. NORMAN. The Chair of the board and myself, and I am not sure whether the Chair actually did it, but I know I myself called one of our attorneys who felt that this was not a criminal assault. This board——

Mr. EVERETT. Did he think it was criminal battery?

Dr. NORMAN. I think what he specifically told me is he did not think that this would merit charges being brought by the U.S. Attorney against Dr. Sager.

Mr. EVERETT. That is not saying it was not criminal assault.

Dr. NORMAN. That is what I recall. That was over 3 years ago.

Mr. EVERETT. I just have to ask you directly—in my estimation, I agree with some of those folks that came to you. I don't understand why Dr. Sager was not fired. Can you give me your reasons why he was given the ten day suspension, and was not fired?

Dr. NORMAN. Again, based on the board of investigation, based on the recommendations of the members, they recommended measured response, not firing him.

Mr. EVERETT. Well, why would they—the VA in its written statement, which you all have said that you accept, has said that this could constitute battery, and battery is a criminal assault. So, in view of that, why would they recommend imposing what I view to be a light sentence?

Dr. NORMAN. We would have to ask the individual board members, but their thinking was one, that Dr.—now I am just trying to recall some of the things that the Chair of the Board told me. One, Dr. Sager was relatively young. Two, this was the first time Dr. Sager had been in trouble. Three, he was a nationally-known, well respected cardiologist, and no one ever impugned his excellence as a physician in clinical care, and——

Mr. EVERETT. The first rule of a physician is do no harm?

Dr. NORMAN. That is true.

Mr. EVERETT. Was this not a high risk procedure that was performed?

Dr. NORMAN. Well, again, my understanding was these were clinical procedures, which had a research component. These were very ill patients.

Mr. EVERETT. There is no cardiac procedure that lasted 105 minutes or 110 minutes, whatever it was, was that not a moderate to high risk procedure?

Dr. NORMAN. I think the clinical procedure moderate to high risk, yes.

Mr. EVERETT. Then, to extend that, seems to me, would be high risk?

Dr. NORMAN. It could potentially harm the patient, that is true. I think you are right.

Mr. EVERETT. Doctor, in all due respect, you are Chief of Staff there, and you agreed with the board's finding?

Dr. NORMAN. I agree with the board's finding, yes.

Mr. EVERETT. Are you still comfortable with that?

Dr. NORMAN. I would have to think about that. I can only say that, based on the board of investigation, based on the evidence, based on reviewing the cases at the time, that was my feeling that I agreed with the board.

Again, initially I thought we should have recommended termination of Dr. Sager. But, I did read the report carefully; I did talk with a lot of people; and, this was what I felt was the right action in 1996. I think in 1999, I think I might have a different opinion about it if it was today, and we were doing the same investigation, it might be different. But, it is hard to say.

Mr. EVERETT. Well, finally, I am not going to belabor the issue, but I would like for you or anybody on the panel to explain to me why this was not criminal assault. Mr. Clark?

Mr. CLARK. I can't provide that explanation, other than to reiterate what Dr. Norman said, and that is, we did in fact, consult with regional counsel at the time. Their explanation to us was that they did not see a criminal act committed here, so we dealt with it administratively in light of that advice and counsel.

Mr. EVERETT. Even though California law says that this a \$10,000 fine and a year in jail?

Mr. CLARK. That was not a fact known to me at the time. I would assume that was considered by regional counsel. I don't know that specifically. But again, their counsel at the time was that this was not a criminal act.

Mr. EVERETT. Did you take into consideration the concept of common rule in making this decision?

Mr. CLARK. No, not specifically.

Mr. EVERETT. No common rule? We were talking about common law and common rule. I am referring to common rule on the ethics of research concerning patients.

Mr. CLARK. The results of the board of investigation, and a variety of other factors were considered in determining what would be an appropriate action. As Dr. Norman indicated—there was a consultation with the hospital ethicist, so ethical issues were included in the analysis that led to the recommended disciplinary action.

Mr. EVERETT. I hope the members will excuse me, and let me have another question or two.

This will not be on the doctor's record permanently, will or will not?

Mr. CLARK. My recollection was that the agreement was it would be part of his official personnel record for a period of 3 years. If there were no further problems that developed that that would be expunged from the record.

Mr. EVERETT. Mr. Clark, this is my last observation. You are an attorney and it would seem to me that under common law, that this would qualify as an assault by definition. Mr. Buyer?

Mr. BUYER. Mr. Chairman, I think you are accurate. If a crime occurs, and then after the incident, an individual provides safe harbor to the alleged criminal, and in that safe harbor, they also obtain knowledge that a crime had occurred, yet they do nothing about it, they become accessories after the fact, and are subject to criminal culpability themselves. So, your questions are very good.

But, I have got some—I want to be constructive in this because I don't want to be overly critical. Your board, is there a counsel, is there attorney representation at this board?

Mr. CLARK. No.

Mr. BUYER. Looking back on it, and I will use my analogy, when you hold your boards at your hospital on quality assurance or risk management, do you have counsel representation at those boards?

Mr. CLARK. There is counsel representation on a number of the medical center committees—not all of them, certainly—but a number of them, the major committees.

Mr. BUYER. Do you have counsel representation of the quality assurance and risk management?

Mr. CLARK. I am not at the Medical Center, so I can't answer that question.

Mr. BUYER. You used to be in charge there?

Mr. CLARK. Yes, when I was the Director.

Mr. BUYER. When you were in charge there, did you have lawyers present?

Mr. CLARK. The attorney was not present on the quality council; he was present for the executive committees.

Mr. BUYER. Doctor Norman, what happens now? Do you lock the lawyers out?

Dr. NORMAN. No, we frequently consult with them.

Mr. BUYER. But you don't let them in the room during the discussions?

Dr. NORMAN. In some boards, we do actually, that I recall. We have actually had attorneys present, and certainly, the witnesses often bring their attorneys.

Mr. BUYER. Mr. Chairman, I hate to rely on personal experience from a past life, but I also was an attorney for a hospital, and served on the quality assurance and risk management. I understand the protective nature within the camaraderie of the physician community, and the high sensitivity about taking actions against another colleague who had exercised particular judgments. It happens in ERs a lot, and so they are very cautious about that.

But in the areas of medical research, when there is a modus operandi and errors of judgment like that, I look at it a little more egregious, a lot more egregious. I am concerned that counsel wasn't participating in this. So, I am going to ask some questions about this.

There was a settlement, was there not, with these four? Did you ask these questions about the settlement, Mr. Chairman?

Mr. EVERETT. No, I did not.

Mr. BUYER. Doctor Norman, you settled with the four veterans that did not have the consent where this procedure was performed by Dr. Sager? Was there a settlement?

Dr. NORMAN. There is no settlement; there was no lawsuit, to my knowledge, from the veterans. They were informed of what happened.

Mr. BUYER. All right. I thought there was a lawsuit.

Dr. NORMAN. No, not that I am aware of.

Mr. BUYER. Were the veterans informed about the disciplinary action taken against Dr. Sager?

Dr. NORMAN. I would have to go back and look at the letter, what the actual letter said that was written to the veterans. Again, that was written 3 years ago. I have it with me. I could go through my files, and look again at it.

Mr. BUYER. Do you think that the veterans have a right to know that disciplinary action was taken against the doctor?

Dr. NORMAN. Yes, I do.

Mr. BUYER. I would like for follow-up to the committee as to whether that was done. I would also ask you that procedures went beyond their informed consent, were the veterans ever informed about the risks associated with the extra time that went in? Have they been brought up to date about exactly what had happened, and the threats to their bodies?

Dr. NORMAN. I don't know. I would have to look at the letter, and I would have to talk to the veterans on the telephone.

Mr. BUYER. Who drafted this letter of—whether it is disciplinary or settlement action—of the dispute with Dr. Sager?

Dr. NORMAN. That was done by human resources.

Mr. BUYER. By human resources? Was counsel by the VA ever brought in to draft this disciplinary action with the doctor?

Mr. BUYER. Wait a minute. I don't know, I don't think so. You are in charge, were you not? Weren't you the responsible party here to carry out the disciplinary action?

Dr. NORMAN. Technically, yes.

Mr. BUYER. Technically, yes. You would know whether counsel drafted it or not. Did counsel draft it?

Dr. NORMAN. I don't think so. It was drafted by our human resources department.

Mr. BUYER. Okay. But, what you don't know is whether counsel took a look at it after it was drafted, is that what you are not sure about?

Dr. NORMAN. I don't know. That is what I am not sure of. I am not sure whether or not the representative from human resources discussed it with counsel.

Mr. BUYER. Right. I want to be very careful about any form of accusations that would impugn your integrity, Doctor. It is easy to go, "You know, these are the docs again, trying to take care of their own." They just want to slap him on the hand and let this thing go away.

When those types of things are done, then it begins to impugn the integrity of the entire system, the VA itself. So, I want to be very careful. I want you to know that, from my perspective, I think it is very, very serious for a doctor to go beyond his jurisdiction, beyond the consent, and to sort of free-lance. Now, it isn't, necessarily free-lance because that data is going to the benefit of someone.

So, Mr. Chairman, I have one follow-up question, if you may?

Do you know who the benefits were going to? Were they going to NIH? Or, were they going to any private source?

Dr. NORMAN. During that time, Dr. Sager's funding was entirely from the private sector, or at least that is what our investigation showed. So, the data would be given to whomever sponsored the research.

Mr. BUYER. Do you know who sponsored that research?

Dr. NORMAN. I could find out. But, I do not know, offhand, which companies sponsored the research.

Mr. BUYER. From a protectorate standpoint, the VA, the protectorate of the veterans' community, that is even more egregious to think that we would permit private sources—I guess, I would hate to say one is worse than the other, but whether it is from Government sources or even from private pay, to gain access to our veteran base for research beyond consent is extraordinarily egregious, in my judgment. Perhaps, you and the board, felt differently. But, I think it is pretty extraordinary.

If you could answer that question as to who derived the benefit from his research to the committee in a follow-up question, I would also appreciate that.

Thank you, Dr. Norman.

Mr. EVERETT. Thank you. My apologies to Dr. Snyder. I will get to you in just a second. But, let me now recognize our ranking member.

Ms. BROWN. Just a couple of quick questions. Gentlemen, no one in this room thinks that the West LA has handled research well, unless it is one of you. Are you being treated unfairly? Is there something here that we don't know about?

Dr. NORMAN. I would like to try to answer that. That question, are we being treated unfairly. I don't think so, but we have to understand that this particular investigation in cardiology was our first, at least my first as Chief of Staff investigation of any scientific misconduct. It is the only allegation up to now, at least until the recent few days, of scientific misconduct. We supervise over 300 investigators who perform a thousand projects a year; so this is a very rare occurrence. I can assure you all that research is conducted overwhelmingly in the highest ethical fashion. Remember, this is the same VA that developed the CAT scan, the same VA that developed advanced forms of dialysis, the same VA that came up with the nicotine patch for nicotine addiction, and the same VA that developed some of the medications which we all use to prevent GI distress. So, we are very proud of our research tradition, and very proud of our research.

However, as the gentleman just referred, we did think this was an egregious breach of ethical conduct. We did think that this particular cardiologist did breach boundaries, and we thought it was extremely egregious. That is why we had a board of investigation, and that is why we carried out the recommendations of the board. At the time, we thought we were doing it correctly.

Ms. BROWN. Well, I don't know if you heard my opening statement, but I did commend VA for their research, and mentioned how we have all benefitted. But, I want to make sure that the safeguards are there to protect the veterans, particularly, the elderly veterans, the minority veterans, the poor veterans. You know, this is their only source of treatment. This is their healthcare, they don't have an option.

Dr. NORMAN. Well, I completely agree with you, and I thank you for your appreciation of VA research. My own interest in research is in geriatrics and elderly veterans and in minority veterans, so I applaud your interest and concern.

Ms. BROWN. In your testimony, you noted some ways in which VA central office was unable to support involvement in the West LA operational manual. Could you discuss this a little bit further?

Mr. CLARK. There a number of ways that the VA headquarters in the office of research, which has been directly involved in this from the beginning, has worked with the network and with the facility in instituting corrective measures.

I would defer to Dr. Feussner, who will be on the next panel to address your question specifically, and he is able to do that.

Ms. BROWN. Okay, and my last question—what do you want to let us know about cocaine research project at West LA? Doctor Pandol?

Dr. PANDOL. Yes, there was a project at West LA until the beginning of 1998 that was funded by the National Institute of Drug Abuse, and the purpose of the project was to develop medications that could be given to patients who had cocaine addiction to see if those medications would decrease the craving so that they wouldn't—obviously, to cure the addiction.

That was a particularly difficult project for us at West LA. I will try to explain it a little bit. We, in the research service during our first year of management of that project, were accused of losing approximately \$900,000 out of a total annual budget of \$1.8 million. VA Washington, VA headquarters, and NIDA management did a joint audit, and demonstrated in that joint audit that the \$900,000 difference was not correct, and it was actually a \$3,000 difference.

However, because of that, Dr. Feussner put our research service on probation. There are other issues that are relevant with the NIDA project. Particularly problematic for me is that NIDA management in Washington argued strongly that they wanted to have oversight over the human research from their vantage point, from Washington, rather than allowing us locally to do that.

That created a problem because we punished by VA headquarters, and then NIDA was arguing with us about oversight. So, we felt in a very vulnerable position in terms of managing the project.

Ms. BROWN. Thank you. Thank you, Mr. Chairman.

Mr. EVERETT. Thank you. Dr. Snyder?

Mr. SNYDER. Thank you, Mr. Chairman.

Doctor Pandol, the specific case that Dr. Sager was involved in has gotten a lot of attention here today. Was that electrophysiologic mapping, is that what he was doing?

Dr. NORMAN. That was part of it, yes.

Mr. SNYDER. So, he had patient consent to do a cardiac cath, correct, is that what it was?

Dr. NORMAN. Yes. And, he extended it to do the mapping. That was the——

Mr. SNYDER. Did he have any consent to do any mapping at all?

Dr. NORMAN. In this one case, he did not, the one case that was investigated by the board.

Mr. SNYDER. So, he had consent to do a——

Dr. NORMAN. Routine electrocardiographic procedure, clinical procedure, not related to research.

Mr. SNYDER. Right. It was a dye study, is that what you are saying?

Dr. NORMAN. Well, it is not a dye study. It is a study where an electrode is put into—

Mr. SNYDER. I am sorry, he had consent to do that kind of an electrode study that you are referring to?

Dr. NORMAN. He did. The clinical aspect of it, but he added on a research component, which he did not have consent for.

Mr. SNYDER. Right.

Dr. NORMAN. It wasn't a dye study. It is using an electrode.

Mr. SNYDER. I understand that. I am trying to get to the Chairman's question about battery versus no battery because there was a signed consent to do something that was very similar. I mean, it was about the same except that it was a longer time, is that correct?

Dr. NORMAN. Yes.

Mr. SNYDER. Not to excuse it at all, but that may have been part of the conflict they had when they discussed this with criminality or not.

Now, Dr. Pandol, Dr. Norman referred to this as a moderate to high risk. Do you agree with the characterization that the extension of time beyond the procedure that Dr. Sager had gotten permission for, did that add on additional moderate to high risk or how would you characterize that?

Dr. PANDOL. Yes, I agree. Also, the board—as I recall the board investigation—agrees with that, as well.

Mr. SNYDER. Was that because he was inducing arrhythmias, is that how that was—or was it just the length of time of having electrodes?

Dr. PANDOL. I believe it was just the length of time.

Mr. SNYDER. Which would make at risk of arrhythmia, I assume that would be the risk?

Dr. PANDOL. Yes.

Dr. NORMAN. Also, the longer a catheter is in, the more risk for infection, and other complications related to anesthesia, et cetera.

Mr. SNYDER. I understand. Thank you.

Is it the routine, Dr. Pandol, for the attending researchers like Dr. Sager to get the informed consent? Is it considered appropriate for cardiac fellows to get the informed consent? Is it appropriate for residents to get the informed consent? How far down the chain does it go before you consider it not appropriate as to who obtains informed consent?

Dr. PANDOL. For research, it is the investigator or co-investigator.

Mr. SNYDER. That would not include your cardiac fellows?

Dr. PANDOL. That is right.

Mr. SNYDER. And, Dr. Norman, there were discussions earlier today about the inadequate resources that are put into these IRBs. What are your comments on that—I assume you heard that testimony earlier today?

Dr. NORMAN. Yes, when we looked recently at the UCLA system and how they adjusted their IRBs, we found that they require minimally four very high level people for each IRB. We had considerably less than that. In fact, Dr. Pandol brought it to my attention, to everyone's attention, that he felt that the IRB process, in order to work better, be more streamlined, needed additional staff.

But also, in fact, our research foundation did vote money over the years. Specifically, this year, something like \$187,000 were voted to improve the staffing for the institutional review boards.

Now, that doesn't excuse in any way, shape or form, the serious matter of the institutional review boards meeting without quorums or not having a community member or their subject matter member. That is a very serious issue. That is something that wasn't known to myself. But, we all know that if you don't have a quorum, you shouldn't have the meeting. Whether you are understaffed or not, that shouldn't have occurred. That was our mistake, and that is why OPRR took their dramatic action. Invalid meetings occurred for a brief period of time. Dr. Pandol, certainly, corrected that in August, but that was known just to the research service, not to anybody else; there had been some meetings that did not meet the criteria of OPRR, and that is a very serious matter. That should be independent of how much staffing you have. You should not have a meeting. But, what that does generate—and I want everybody to understand that—there is tremendous pressure on the IRBs to return in a timely fashion their approval or non-approval of investigators' projects. In fact, at the West LA facility, I should report to everybody that investigators complain to me regularly that the institutional review boards were too thorough, too picky, required too much changes, and took too long. So, that is why—at least from where I was sitting—I was shocked at the events with OPRR because I assumed we had a very good process. And, my own protocols which I put in were gone over with a fine-toothed comb by the institutional review boards. So, by and large, they did a good job. However, there was a serious lapse, there is no question about it; and, it should not have happened. How IRB chairs did not know that you cannot have a meeting without quorums? I don't have an answer for that.

Mr. SNYDER. I forget what the characterization is, was it the culture of sloppiness that existed, and some implication that it still exists? Do you agree? I assume you don't agree with that characterization? How would you define it? Are you a recovering sloppy?

Dr. NORMAN. No, we are recovering by paying excruciatingly good attention to detail. We are recovering, and I think, have dramatically changed the culture. You know, we are in part of the—when you think about when these disasters happen, and this is nothing short of an earthquake, an earthquake through our research service. There is plenty of blame to go around. I will, certainly, accept a lot of that. I am sure Dr. Pandol will, as well. But also, the whole system has to take blame, including the investigators themselves. Who did not show up for these IRB meetings? It was the investigators. They are the ones that did not show up. In fact, for some institutions, UCLA told me, that when an investigator doesn't show up, they publish his or her name to the other investigators to let them know that is why their protocol did not get approved. That is a policy we will have shortly.

Mr. Norby has been leading the recovery effort, and can give you a lot of details of all the steps that we are taking to make sure that we are doing things right.

The other issue that came up was the data safety management board. That board did meet, at times, and Dr. Pandol probably has

more to say about it. In 1996, somehow, it dropped. But the data safety management reports—these are the reports that are done to ensure that our vulnerable populations, our seriously mentally ill, patients with dementia—can truly understand informed consent and give informed consent. What is done at our institution, and actually the people involved, Drs. Marder, Wirshing and another person, just published an article on how to ensure that seriously mentally ill patients could give informed consent. Dr. Marder has met with me on several occasions telling me of all the advances. The investigators give the patients tests; the patients have to pass the test, in order to be able to enter a research project. These data safety management reports were prepared. But, unfortunately, there was no board to look at the reports. So, the monitoring data was collected. There appeared to be no problems with the process, and I heard nothing but good things about how well it was doing. What I didn't know was that there was no data safety management board, an additional process to look at these reports. The Board was needed to ensure that patients—these are patients in whom their own physician may, in fact, be the investigator, which creates an ethical conflict were protected. There was no reason to think that these reports were not going to a data safety management board. I really didn't know that it wasn't meeting until March 22, when OPRR informed us.

Mr. SNYDER. Mr. Chairman, may I ask one short question? I am sorry.

During your time there, as you look back now from this perspective of 20/20 hindsight, again going back to this metaphor, "the culture of sloppiness," what periods of time, if any, do you agree with that characterization, at a time when you have been Chief of Staff, that there has, indeed, been a culture of sloppiness with regard to the investigation things we are talking about today?

Dr. NORMAN. I don't perceive a culture of sloppiness. I think some individual investigators, certainly, are sloppy. In one case, one person crossed way over the line as far as sloppiness. We had some unethical behavior, and we have already talked about that. What do I think happened? Again, as physicians, we talk about the retrospectoscope, looking back through a scope in time, and changing your judgments. Brentwood VA Research Service and Wadsworth VA Research Service—remember we were two VAs under the West LA campus—merged around 1996 about the time Dr. Pandol came. I think, at that point, when the research services merged, somehow it was not transmitted that: one, we needed quarterly reports to go to OPRR as part of our restriction; that was our sole restriction, and that wasn't transmitted, apparently, to Dr. Pandol. There were many people in the research service that were still around, and it is hard for me to understand that. I think the data safety management board also, for the same reason, fell apart at that time. So, something in that reorganization created a period of laxness, sloppiness. Then the IRBs, for those few months actually started meeting without quorums. That suggests to me a lack of education, turnover in chairs, et cetera. But, certainly, we did not pay proper attention to the IRB process, there is no doubt about that.

Mr. SNYDER. Thank you.

Mr. EVERETT. Thank you. Chairman Stearns?

Mr. STEARNS. Thank you, Mr. Chairman. I just wanted to go into the accountability. Once you find a person who has crossed the line, either malfeasance, or failure to seek consent forms, for example, do you feel you have, within the facility, the means to discipline these people? Do you feel you can fire a person? Do you feel you can suspend them? The view that we have up here is that VA managers show a little hesitancy to take disciplinary action. I think the individual involved was suspended for 10 days, but only did seven. You are going to go back and address the remaining three. Why in the world are you so hesitant about this? Why isn't there pretty strong action on your part, where something is done quickly, permanently, and sets an example for others?

Dr. NORMAN. Well, first of all, I think that we certainly try to do that. I thought the action had been taken, and it was only in the last few days I found out that he hadn't served the full 10 days.

Mr. STEARNS. Let me ask you, why didn't he serve the full ten days?

Dr. NORMAN. Well, I think that—I haven't read completely the investigation that was done, but his own accounting is that he thought he did serve the whole ten days. But, when we looked at his pay records, pay was only withheld for seven days. That had to do with the follow-up by his service and service chief. Mr. Norby knows it better than I do. Maybe you could comment?

Mr. NORBY. There was just not the follow-up by the appropriate individuals within the service to make certain that the time records had been appropriately recorded, that he had actually served the time, and that was documented. That was the issue.

Mr. STEARNS. From my perspective, it looks like there is sloppiness, that Dr. Snyder talked about, in the enforcement of the regulations. Then, there seems to be a lack of commitment to even enforce, once these regulations are degraded and they are not executed. So, it seems like all down the line, there is a tentative approach here. It seems like the official responsible for disciplining this individual would have said, "You are fired, or you are suspended," and would have known whether the person was suspended the full ten days or not.

Mr. NORBY. You are exactly right, and that person should have known that. That person didn't follow through, and there will be appropriate corrective actions taken with those individuals.

Mr. STEARNS. So, not only do we have to discipline the person who is culpable; then you have got to go back to the person who was supposed to monitor it; and, that person is lax and tentative, and that is systemic of the whole operation here, just as an observation of an outsider.

It doesn't seem that there was any sense that something that happened was so outrageous that we are going to make sure that this person is disciplined, and that the discipline is properly administered. It is hard for me to understand that, once a person did something like this, that everyone would be lax on the discipline.

Mr. CLARK. Perhaps I can respond since, at the time, I was the, ultimately the accountable official at the medical center.

I wanted to go back to your question about whether we felt there was the authority present to take the full range of disciplinary ac-

tions, and certainly, there is. Ultimately, when a board of investigation is completed, and they make some recommendations, and it goes through a series of subordinate officials for their review and recommendation, we view the case in the entire context of the facts and the environment, and are guided by a range of penalties. In this case, it would appear as if, at least, we were dealing with endangering the safety of a patient and possibility of patient abuse. The range of penalties there would be from a reprimand to discharge. The action that was taken was a ten day suspension, which is by definition, a serious adverse disciplinary action. So, again, under the circumstances, considering all of the factors, it seemed like that was the appropriate action to take. But clearly, there was the authority to take the entire range of penalties that are contained in the range of penalty guidance.

Mr. STEARNS. Can you sit here this morning, and say that the actions taken have been executed and that this individual is going to be suspended for ten days? Do you know for a fact today, whether he is being suspended for ten days or not?

Mr. CLARK. My understanding is that there is a group that has been reviewing that issue. It appears as if he did not take the full ten day suspension, and that action is being instituted to ensure that the remaining days of suspension are acted on.

Mr. STEARNS. For us, then, when we see this tentativeness on discipline, then the next question is who is going to monitor this person's research? If the person feels that you are tentative, and he comes back on the research, what procedures are you implementing to make sure that you monitor this person's research, and what he does hereafter?

Dr. NORMAN. Can I answer that, since we have taken that action?

Mr. STEARNS. Sure.

Dr. NORMAN. Again, after the initial board of investigation, Dr. Sager was closely monitored for a period of time, well over a year.

Mr. STEARNS. By whom?

Dr. NORMAN. By Dr. Pandol. Second, there have been recent allegations about Dr. Sager. This came from, actually, Dr. Sager reporting to me that a newspaper reporter had questioned him about new cases that were brought to the reporter's attention from the cardiology staff. As soon as Dr. Sager gave me the names, I reviewed the research charts, and looked at them and felt there were some questions about inclusion criteria for his studies. So, we have another board of investigation, this one done entirely by outside people, not in our facility, that are looking at his research.

Now, in the meantime, as in the first investigation, we had concerns that since Dr. Sager was under a new investigation, that there be somebody monitoring the way the research is done. Now, no new patients would be entered in his study, that is part of the VA directive, part of our research suspension.

But, what about the 60 seriously ill patients that are in Dr. Sager's study right now? What we have done is we have hired an outside electrophysiologist to supervise Dr. Sager in caring for the 60 patients that are in his studies right now. That person is in place, and doing their job, and we will see what—the current investigation is ongoing. We will see what that investigation shows.

Mr. STEARNS. Has his behavior and incident been reported to the licensing board?

Dr. NORMAN. The original incident was not reported to the licensing board.

Mr. STEARNS. And, why hasn't that been reported? Is it inappropriate to report it?

Mr. NORBY. At that time, we did not have the authority to report a continuing employee to the licensing board. That has, since, changed.

Mr. STEARNS. Are you going to report this to the licensing board?

Mr. NORBY. It will depend upon, obviously, the results of the investigation that is ongoing right now, and what they find.

Mr. STEARNS. Thank you, Mr. Chairman.

Mr. EVERETT. Thank you. We have another vote going on. Let me just, briefly, say in response to some of Dr. Snyder's remarks and great questions. It seems to me, once you go beyond common rule, you violate ethics and patients' rights. Further, as a matter of common law, once you go beyond consent, that is where battery begins, at that point.

I want to thank this panel, and that will be all for this panel. We will recess for about 15 minutes.

[Whereupon, the subcommittees recessed for 15 minutes.]

Mr. EVERETT. Dr. Kizer, would you, please, introduce your staff? After that, I would ask you all to rise.

Dr. KIZER. To my immediate right is Dr. Jack Feussner, who is the Chief Officer for Research and Development, and next to him is Dr. Tim Gerrity, also with the Research Office.

Mr. EVERETT. Would you all, please, rise?

[Witnesses sworn.]

Mr. EVERETT. Thank you. Please be seated.

Dr. Kizer is Under Secretary for Health, Department of Veteran Affairs. We will now proceed with your statement.

TESTIMONY OF KENNETH KIZER, M.D., M.P.H., UNDER SECRETARY FOR HEALTH, DEPARTMENT OF VETERAN AFFAIRS; ACCOMPANIED BY JOHN FEUSSNER, M.D., CHIEF RESEARCH AND DEVELOPMENT OFFICER, DEPARTMENT OF VETERAN AFFAIRS, AND TIMOTHY GERRITY, M.D., SPECIAL ASSISTANT TO CHIEF RESEARCH AND DEVELOPMENT OFFICER, DEPARTMENT OF VETERANS AFFAIRS

TESTIMONY OF KENNETH KIZER

Dr. KIZER. Thank you, Mr. Chairman and members of the subcommittees. Thank you for the opportunity to be here today to discuss current issues related to VA's research program, and I ask that my complete testimony be accepted for the record.

Mr. EVERETT. Without objection.

Dr. KIZER. I recognize the time is limited, so I am going to abbreviate my planned opening statement. However, I want to clearly and unequivocally state that the standards for research conduct within VA are, at least as comprehensive and, indeed, in most cases, more comprehensive, than the other 16 Federal agencies who are also bound by the regulations governing the conduct of research involving humans.

I also want to stress that research is a very important part of VA healthcare. In conducting research, it is paramount that respect for the rights and the dignity and safety of research subjects be the top priority. There really should be no question that all VA research, human, animal or laboratory, will be performed in accordance with the highest of ethical standards.

There have been a variety of comments earlier this morning that, because I was in another hearing, I missed. But, from what I understand, many of the efforts that VA has underway to oversee research have been commented on in one way or the other.

I want to focus the next couple of minutes on two new initiatives that we are embarking upon, as well as the very important question before the committee as to whether the problems that have been identified at the Greater Los Angeles Health Care System are an isolated occurrence, or do they represent a serious endemic problem within the whole research system. I certainly have no evidence or basis to believe that the problems which have been described at LA are widespread or prevalent throughout the VA research program.

However, I also have to say, and in hearing some of the discussion this morning about oversight for research, I do believe that it is time for research everywhere, including VA, to make a more comprehensive and systematic effort at overseeing and building in accountability.

It is with that in mind that I comment on two new major initiatives that we are embarking upon. The first is the creation of an independent office of research compliance and assurance. The second is the identification and selection of an external accreditation body for our research programs, in general, but especially those that involve human subjects. I should also stress that there are no models for this outside of the VA. By embarking upon these new initiatives, VA is clearly setting a new standard for research accountability.

The new Office of Research Compliance and Assurance will report directly to my office. It will be, in many ways, similar to the Office of the Medical Inspector. The primary mission of this office within VHA will be to assure that the research conducted by our scientists across the country is done with maximal regard for issues of human and animal subject protection, for safety of laboratory personnel, as well as for the integrity of the research process. I want to emphasize that this new office of Research Compliance will be an independent, objective, and unbiased entity in its compliance and oversight activities.

I am reminded that GAO in one of its reports has criticized the placement of OPRR within the National Institutes of Health because of concerns that this internal placement might hamper its independence and some of its oversight activities. By placing the Office of Research Compliance outside of the Research Office, and directly reporting to top management within the Veterans Health Administration, it is my intention to minimize any real or perceived weakness of this type.

With regard to external accreditation, as you well know, all of our hospitals are accredited by the Joint Commission on Accreditation of Health Care Organizations. We also have a similar process

for our animal facilities. But, there is no such process or comparable mechanism for institutions conducting research involving human subjects. We will, in the very near future, be publishing a notice that seeks to identify such an external entity to serve as an accrediting body for our research programs, and for our institutional review boards, in particular. I think that through this action we will actually become the driving force to establish an accreditation entity, and an accreditation process for research involving humans. That does not now exist, and our effort will, I believe, set a new standard for research accountability.

I see the red light is on, so with that, let me defer any further comments, and try to address questions that you or other members may have.

[The prepared statement of Dr. Kizer, with attachments, appears on p. 112.]

Mr. EVERETT. Thank you very much, Dr. Kizer. I have read your statement, and you have commented on the new proposals for research compliance, and that will be a matter for the record.

Let me ask you, when did you become aware of the problems with West LA research?

Dr. KIZER. I became aware of those problems on March 19. It was shortly before the letter was dispatched to the facility. I don't recall which days of the week those were, but as I recall, this came up on a Thursday or Friday, and a decision was made to move forward with the suspension of research activities. I would have to check the calendar for the exact dates that correspond to that.

Mr. EVERETT. What I am driving at, Dr. Kizer, is the fact that it seems to me the problems weren't effectively or timely addressed. Your research people in Washington knew about the problems at West LA from almost the very beginning. That is my understanding. Why wasn't this handled quickly, and who is responsible for that?

Dr. KIZER. I will turn to Dr. Feussner or Dr. Gerrity to respond to that as they see fit. I would note that Dr. Feussner was the one who came up to my office, as I recall, on Friday, with the information. I think he can attest to the reaction that that elicited.

Mr. EVERETT. Let me put the question to you, Dr. Feussner? When did you first learn of this?

Dr. FEUSSNER. When did I first learn of the problems in West LA?

Mr. EVERETT. The problems in West LA, including the cardiac case that we referred to so often today?

Dr. FEUSSNER. I became aware of problems in West LA in the early part of 1997, when I—

Mr. EVERETT. You were not aware of any of the problems as early as back in 1993?

Dr. FEUSSNER. That is correct. I became aware of the problem with the specific issue in cardiology when asked a question by the media recently.

Mr. EVERETT. Let me ask you a question. The protections for veterans in the research has no medical benefit for them, or could be harmful to them?

Dr. FEUSSNER. Well, let me be sure I understand your question. The question relates to human research that doesn't involve any-

thing to do with treatment? So, there is nothing involved in treatment.

Mr. EVERETT. When the veteran has no benefit from it?

Dr. FEUSSNER. I think the protection for the patient under those circumstances is twofold. First is that the research being conducted is meritorious, so the first part is a review process that passes on the merit of the research project, as a scientific endeavor.

The second part of protection for the patient, then, is a patient is informed, or that information is appropriately disclosed that indicates what the potential benefits are. If there are no potential benefits, that is stated, and then, what the risks are. Then, the patient, as you have discussed earlier today in the process of informed consent, is informed about the risks and the benefits, and either consents or does not consent to participate in the research.

Patients who are impaired, or who are incompetent, cannot give informed consent. And, under the circumstance where the patient cannot give informed consent, that informed consent must be obtained by some surrogate mechanism, say from a duly appointed—someone who is a duly appointed power of attorney, et cetera.

Mr. EVERETT. How long have you been in charge of VA research?

Dr. FEUSSNER. Since August of 1996, I believe.

Mr. EVERETT. Without identifying the individual veterans, what happened in each of the cases in West LA where research was performed without the veterans' consent—the four cases?

Dr. FEUSSNER. The situation, as I became aware of, involved cardiology research, and involved allegations of doing research in the absence of informed consent, and involved at least three separate individuals. The allegations of failure to obtain informed consent, or investigate it, and in two cases, I believe, the allegations for unethical conduct were upheld. So, in two cases, physicians were identified who had proceeded forward with research process without getting appropriate informed consent. In one of those cases, it would appear that the patient actually declined to give informed consent, and the procedure was performed anyway.

Mr. EVERETT. I believe he declined twice, did he not?

Dr. FEUSSNER. I think that is correct.

Mr. EVERETT. Can human research, without consent, constitute patient abuse?

Dr. FEUSSNER. Yes, I think research that is conducted on patients without their consent can.

Mr. EVERETT. How about battery or criminal assault?

Dr. FEUSSNER. Well, I am not a lawyer. I did listen to the discussion this morning, and I think it is also possible that if you do something to a person that a person does not want you to do, that that is improper.

Mr. EVERETT. Dr. Kizer, I am failing to understand something here. I am told that Washington was copied on the problems with West LA VA research as early as 1993. Is that not correct?

Dr. KIZER. I can't attest to that. I have heard that, as well.

Dr. FEUSSNER. Yes, sir, I can answer that.

Mr. EVERETT. Please.

Dr. FEUSSNER. Yes, sir, I think the answer to that question is "yes." I believe in 1993–1994 and 1995, communications from OPRR were copied to VA research headquarters.

Mr. EVERETT. And, that didn't trip a wire to somebody that somebody needs to go take a look or do something to see what is happening out in West LA VA?

Dr. FEUSSNER. I don't know the answer to that question. There was a liaison at the time between VA research and OPRR; there was an awareness in VA research that this information had been communicated. But, I can't comment on what the VA research leadership thought or did with that information. I was not aware of what decisions they chose to take or not.

Mr. EVERETT. Here is what I am having a problem dealing with. Apparently, the VA subscribes to common rule, is that correct?

Dr. FEUSSNER. That is not apparent, sir. That is absolutely "yes."

Mr. EVERETT. Okay. These violations beginning in 1993 were a violation of common rule, were they not?

Dr. FEUSSNER. Yes the common rule depends on appropriate assurances being in place so that a funding organization knows that appropriate steps, appropriate safeguards are being taken. And, when those assurances are not in place, there is no evidence, therefore, that patients are being appropriately protected.

Mr. EVERETT. My problem is that it seems a number of years went by before anybody really did anything out at West LA.

Dr. FEUSSNER. Well, yes, I think 6 years, to be precise, went by without people taking, perhaps, more assertive action.

I would say that when I came into headquarters I was not aware of those prior OPRR communications. It is unfortunate that, in the period of time from 1996 until this year, that subsequent communications between West LA and OPRR were not copied to us. Our communications with OPRR have not been optimal. We have increased—we have taken efforts to improve those communications. We have formed a liaison function between VA Research Headquarters and OPRR, have attended several meetings at OPRR, and all I can say is that that information was not brought to our attention, and I think that is a failure of the communication.

Mr. EVERETT. Are you aware of any other VA research facilities where we have had complaints like violation of common rule over a period of time of 5 or 6 years?

Dr. FEUSSNER. With the exception of the information that you heard this morning concerning investigation of the Bronx VA, and investigations that have begun in a very recent time, no, I am not aware of any.

Mr. EVERETT. Dr. Kizer, I know you well, and I know very well that, as far as the other doctors on the panel, that this is unacceptable to you. I know that you are going to give this committee the assurance that this will not happen again.

I think you also know that I have a real problem with the culture of this VA. For 4 years now, I have seen the tendency of VA not to hold people responsible. We can go to the Columbia situation; we can go to Tuskegee situation; we can go to the North Carolina situation with Mr. Calhoun. It just seems to occur over and over again. What assurances can you give this subcommittee that individuals are going to be held responsible for their actions, and that we are going to finally see some tightening of the discipline procedures at the VA?

Dr. KIZER. I think there is nothing about the action that we took on March 22 that was tentative. Indeed, it was taken very quickly, after being informed of the situation.

Mr. EVERETT. You are referring to the suspension, sir?

Dr. KIZER. The suspension. And, in my judgment, that on hearing both the history, that this was something that had gone on for a prolonged period of time, and I don't know that there is any other way that you can characterize it. But, the information was not conveyed to the appropriate levels of the Department, where I think a more appropriate response would have been taken earlier, had we been aware of it. A decision was made; it was acted on; it is, clearly, unprecedented in research anywhere to take an action like this. I think the actions that we are taking now, as far as putting in place new infrastructure and mechanisms also attests to the seriousness and the rigor with which we are going to approach the problem.

Mr. EVERETT. Excuse me, you are talking about the actions of closing down the research facility?

Dr. KIZER. Yes, as well as putting in place the Office of Research Compliance and Assurance, which will have a mechanism to avoid the type of communication failures that were alluded to before, as well as the external accreditation. Again, accreditation of research programs is not a new idea. This is something that has been talked about for at least 15 years. The culture in research, in general, this is not VA but everywhere, has not been supportive of that idea. I think the time has come that we just have to do it, and move forward with it. I am not commenting on the specific individuals; I don't have all the information I need at this point to know what decisions as far as personnel actions may be taken.

Mr. EVERETT. I know you don't mean to say that everybody else does it, so it is okay that we do it, too?

Dr. KIZER. No, that was not what I was saying. What I was saying is that the culture has been such that the type of actions that we are announcing today have not been acceptable in the past. I think that, by the VA doing it coupled with the prominence and the magnitude of the VA research effort, we will, indeed, set a new standard for research conducted everywhere in the country.

Mr. EVERETT. When do you think the research at West LA will be allowed to continue?

Dr. KIZER. Some of it is already back, but let me defer to Dr. Feussner to comment on that.

Dr. FEUSSNER. Sir, we presented a recovery plan to your staff, or some of the committee's staff, on the 25th, I believe, of March. That recovery plan is on schedule, and we have reconstituted the various committees, and we have reinstated approximately 75 percent of the lowest risk research, that is research done not on animals, not on humans, and not associated with any hazardous materials. So, the reconstitution of the research program at West LA has begun.

Mr. EVERETT. Doctor, what is the situation with Sepulveda research and what are the problems there?

Dr. FEUSSNER. I am sorry?

Mr. EVERETT. Have any of the VA research animals at Sepulveda been subject to inhuman conditions or treatment? I am sorry, inhumane conditions or treatment?

Dr. FEUSSNER. No, sir, there are two primary categories of problems at the Sepulveda animal facility. One is a lack of updating of procedures for protecting humans who work with animals from exposures to, say, hazardous biological agents, et cetera. The second is housing conditions that are not always optimal relating to issues of humidity, issues of appropriate temperature, and overcrowding of some rats.

Mr. EVERETT. When will the human research restart?

Dr. FEUSSNER. That is a complex question. Some of the human research was allowed to continue because of safety concerns for the patients. So, when the research suspension was taken, we asked the site to identify research projects, which if stopped abruptly, would potentially be harmful to the patients, and also to identify the same types of projects or, if the research were stopped abruptly, it would either harm the animals or lead to the wastage of the animals' lives. So, some of the human research has continued in the sense that patients already enrolled in studies are allowed to continue in the study and finish. But no new patients are allowed to be entered. The last part of the research program in the greater Los Angeles area that will be reconstituted will be the human research component. I am hopeful that we will be able to start reconstituting some of that within the next 30 days.

Mr. EVERETT. Dr. Kizer, there is clear concern about the capability of the mentally impaired, the elderly, the chronically ill, of the less well and the less educated to provide truly informed consent to participate in research. Do you see a special obligation in VA to take steps that go beyond compliance with Federal research regulations to VA's unique patient population?

Dr. KIZER. I do, as I believe the current VA policy does; the current VA policy is that any individual who is decision-impaired and who may not be able to give a full informed consent can only participate in protocols that are directly related to their disorder, whatever that may be, and, also, that cannot be done if it involves more than a minimal risk to the individual unless there is probable treatment of benefit to the patient greater than any potential harm. These aspects of VA policy are consistent with the recommendations of the National Bioethics Advisory Commission. Also, VA policy exceeds the current Federal standard for research on decision-impaired individuals.

Mr. EVERETT. Thank you very much. I recognize our ranking member now, Ms. Brown.

Ms. BROWN. Thank you, Mr. Chairman. I appreciate, as I said earlier, the contributions VA research has made with aging, alcohol and drug dependency, heart disease, post-trauma stress, and, of course, with women veterans. I have a couple of questions that I want to ask, and I spoke about this earlier.

I am concerned about poor veterans who have no other recourse for medical treatment, except the VA. I have been reading reports of patient consent issues that other facilities—I guess that is another question. Can you answer that first one, first?

Dr. KIZER. If I understand the question, it was in the same vein as what the chairman had asked, that poor individuals who may not have access to other care may feel pressured to participate in something, since that is part of their care. That should not occur;

an individual—and I am taking it that your reference is to individuals who are in full possession of all their decisionmaking abilities—should be accorded the same rights and privileges of anyone else. If they wish to participate, and after being fully informed as to what the project is about, what the potential benefit may be to society and not to the individual itself, and what the risks are to themselves, if they elect to participate, so be it. We owe them an obligation for doing that, but certainly they should feel no obligation and should never be pressured into participating in something because they happen to rely on the system for their healthcare.

Mr. FEUSSNER. Ma'am?

Ms. BROWN. Yes, sir.

Mr. FEUSSNER. May I comment, as well?

Ms. BROWN. Yes, sir.

Mr. FEUSSNER. I would like to say three things. The first is that the common rule was extended by VA in, I believe, February or March of 1998, to include a responsibility in VA for compensation of patients who are injured as a result of participating in research. At this moment, none of the other signatories of the common rule have followed suit with that issue.

Second issue is that one of the critical components of the informed consent process is voluntariness. That is to say, not only do patients have the decisionmaking to agree or not to agree to participate in the research, but at any moment subsequent to that they have an opportunity to stop.

The VA policies on impaired consent—that is, obtaining informed consent from patients who are impaired—I think anticipate some of the recommendations currently available in the National Bioethics Advisory Commission report and were put as part of policy in 1992, and those include issues of obtaining surrogate consent and how that is to be done; indicating that if there are ways to study, if the study does not require specifically the patients who are impaired—say, a study on Alzheimer's Disease—then those patients should not be included in the study, and then an assessment of explicitly accessing the patient's decisionmaking capability.

Now, that later issue is very problematic, in part, because there is so systematic way to proceed with that. In 1997, VA funded an effort that compiled all the empiric literature on informed consent for the first time. The document is of sufficient weight that it was published as a bibliography, not as a scientific paper, in the Hastings Center Report recently.

In December 1998, the VA funded a program called E-QUIC, the Enhancement of the Quality of Informed Consent. Two of the major deliverables out of the E-QUIC initiative, the first of which I expect to have available later this summer, perhaps as early as August or September, is a screening mechanism, a formal screening mechanism, that could be in place that could quickly assess the patient's decisionmaking ability and then stratify the patients based on whether they have impaired decisionmaking or not, for whatever reason.

The second deliverable out of the E-QUIC initiative is to prepare a video that in general describes the research process, tells patients in the video what their rights, privileges, et cetera, are.

So, my sense is that we are dealing with those issues proactively, in addition to which, in our outcomes research component several years ago, we made a specific research priority the investigation of issues relating to gender or ethnic bias in the application of healthcare, and so one of the research priorities within the health services research component is specifically looking at research issues and generating information to see if we can identify situations where there are actually biased bases on gender or on ethnicity.

Ms. BROWN. Mr. Chairman, can I follow up with an additional question?

Dr. Kizer, I found the recommendations of the National Bioethics Advisory Commission about consent of the mentally ill sensible and humane. Is there any plan for you all to make this a part of your common rules and regulations?

Dr. KIZER. As I noted in my response to the prior question, most of those are already part of VA policy, those recommendations.

Ms. BROWN. I would like, Mr. Chairman, to submit to the record a letter from President Clinton, as he is in support these recommendations.

[The letter follows:]

THE WHITE HOUSE, February 22, 1999.

Dr. Harold T. Shapiro,
Chairman, National Bioethics Advisory Commission
Rockville, MD.

DEAR HAROLD: I was pleased to receive the National Bioethics Advisory Commission's report, "Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity." As the report indicates, we must ensure that research on humans is done in an ethically acceptable manner. This requires that the rights and welfare of all human subjects, particularly those that are more vulnerable, be protected.

I have asked Dr. Neal Lane, my Science Advisor, to ensure that all agencies that conduct research with human subjects review the report and respond to the commission's recommendations. He will keep you apprised of the progress of the review as well as deliberations on a future course of action.

I thank you and all the members of the commission for the hard work and dedication that went into preparing this report.

Sincerely,

BILL CLINTON.

Ms. BROWN. Mr. Chairman, before we move on, though, I would like to say that I think, based on we have heard here today, we should hold at least two field hearings, I think, in West Los Angeles for one and maybe in Tampa, which is in Florida, or the Bronx or some other place, because I am really concerned that this problem may not be unique to this situation and it may be broader, and it is our responsibility to certainly support the VA, but also safeguard the veterans.

Mr. EVERETT. We certainly should be able to make some sort of site visits to those two institutions.

Ms. BROWN. Thank you.

Mr. EVERETT. Dr. Kizer, although we often have frank discussions, it is always a pleasure to see you here. I appreciate the work that you and the other VA officials do. I know where your heart is. We may from time to time have disagreements on procedure and policy and that kind of thing, but I do appreciate your appearing

here today, and since you left the Appropriations Committee, I assume that this was really a breeze. (Laughter.)

Thank you very much. We will now have the next panel.

Dr. KIZER. Thank you, sir.

Mr. EVERETT. I would like to welcome Eric Meslin, the Executive Director of the National Bioethics Advisory Commission; Paul Appelbaum, Chairman of Psychiatry at University of Massachusetts Medical School, and Chairman of the American Psychiatric Association Ethics Appeals Board, and Dr. Adil E. Shamoo, M.D., professor of biochemical and molecular biology at the University of Maryland, Baltimore.

Would you gentlemen please rise?

[Witnesses sworn.]

Mr. EVERETT. Thank you. Please be seated.

Doctor, if you will proceed.

TESTIMONY OF ERIC M. MESLIN, PH.D., EXECUTIVE DIRECTOR, NATIONAL BIOETHICS ADVISORY COMMISSION; ACCOMPANIED BY PAUL APPELBAUM, M.D., CHAIR, DEPARTMENT OF PSYCHIATRY, UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL, AND CHAIR, AMERICAN PSYCHIATRIC ASSOCIATION ETHICS APPEALS BOARD, AND ADIL E. SHAMOO, M.D., PROFESSOR, DEPARTMENT OF BIOCHEMICAL AND MOLECULAR BIOLOGY, UNIVERSITY OF MARYLAND, BALTIMORE

TESTIMONY OF ERIC MESLIN

Dr. MESLIN. Thank you very much. Good afternoon, Mr. Chairman and members of the subcommittee. I am Eric Meslin, the Executive Director of the National Bioethics Advisory Commission or NBAC. I am pleased to appear before you this afternoon to describe the recommendations NBAC made in its recent report on Research Involving Persons With Mental Disorders That May Affect Decisionmaking Capacity.

The report's recommendations were approved by NBAC in November of 1998, completed and published in late December of 1998, and forwarded to the President on January 8, 1999, as required by our Executive Order. Since I made copies of the report available to the subcommittee as part of my written testimony, with your permission, I will briefly summarize the report's major recommendations.

Mr. EVERETT. The complete testimony will be made a part of the record.

Dr. MESLIN. Thank you, sir.

Mr. Chairman, as you are aware, there have been previous efforts to extend additional regulatory protections for research involving individuals with mental disorders, but these efforts have not been fully successful. In the late 1970's, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research studied the need for special protections for research subjects with mental disorders in a report on Research Involving Those Institutionalized as Mentally Infirm. The Department of Health, Education and Welfare proposed regulations in 1979, but these were never adopted.

NBAC examined this topic because of the special needs of these human subjects, including the need for more research, but also because of the weaknesses in Federal regulations that have persisted for the past two decades. Several highly-publicized incidents, some of which have already been mentioned in this hearing, involving research subjects in this vulnerable population, were also brought to the NBAC's attention.

NBAC found that important progress has been made by the Nation's scientists on the cause and treatment of mental disorders, and that the scope of research is expanding. Moreover, the research environment has become far more complex, involving both a large societal investment and a greater role for the private sector. NBAC concluded, however, that in addition to the existing Common Rule, "research involving subjects with mental disorders that may affect decisionmaking capacity should be governed by specific further regulations." As Dr. Harold Shapiro, the Chair of NBAC, stated in his letter to President Clinton transmitting this report, "While current U.S. regulations note the need for ethical treatment of human research subjects with mental disorders, they provide no specific guidance for IRBs and investigators regarding vulnerable subjects. We believe that this state of affairs is not satisfactory and that additional Federal protections are necessary."

Mr. Chairman, NBAC made 21 recommendations. Many of them are non-controversial and should enjoy broad support. For example, research should not target people with mental disorders when research can be done with other subjects. Researchers should describe the risks in studies to IRBs, so that IRBs can make an informed risk-benefit assessment, a determination that is especially important when the studies involve placebo controls, symptom provocation, or challenge studies, or rapid medication withdrawal. A subject's objection to participation should be heeded, even if he or she is confused or is incompetent. An IRB should ensure that researchers establish and maintain ongoing communication with the subject's family and friends.

Some of the other 21 recommendations will likely be seen by researchers as too restrictive and by those concerned more with the rights of subjects as too permissive. For example, NBAC's recommendation that, where research involves greater than minimal risk, IRBs should require researchers to obtain an independent assessment of the subject's capacity to consent, may be considered too great an imposition on researchers and institutions; while some might have hoped to see this recommendation go even further, requiring that all research subjects, regardless of the level of risk in a study, be assessed for their capacity. Some will consider NBAC's recommendation that subjects who are capable of consenting can give a "prospective authorization" to their future involvement in research, to be an important method for permitting competent persons to express their wishes for participation in studies in the future when they are no longer able to express their wishes. Others may find that this recommendation permits too many people to be enrolled in research without their expressed informed consent.

NBAC was persuaded that for research involving greater than minimal risk, but that does not hold out the prospect of any direct medical benefit to the subjects, those subjects could be involved

only under the most stringent conditions. In particular, NBAC recommended that the Secretary of Health and Human Services convene a special standing panel to review these protocols at a national level. This panel would include members representing the diverse interests of potential subjects, the research community, and the public. The panel would provide a national and publicly accountable review mechanism for research. It would be charged with developing guidelines that could be used by local IRBs. NBAC recommended that all Federal agencies subject to the Common Rule use this panel and that a study of effectiveness be completed within 5 years. While NBAC did not signal out the Veterans Administration in its recommendations, it did intend for all agencies subject to the Common Rule, including the VA, to consider the Commission's recommendations.

I should add, Mr. Chairman, that NBAC proposed a number of additional guidance proposals, one of which is the use of audit and public disclosure. This appears on page 67 of the Commission's report. They proposed a number of other recommendations for regulatory reform, but did not take a position on whether these reforms would be best accomplished through changes in the Common Rule, Subpart A of the Federal Policy for the Protection of Human Subjects (the Common Rule), or through the adoption of a new subpart in the Code of Federal Regulations.

More importantly, the Commission made clear its belief that some of the changes could be implemented voluntarily at the local level emphasizing the following statement in its report, "Regardless of which regulatory route is selected, NBAC encourages researchers in institutions to voluntarily adopt the spirit and substance of these recommendations."

Like all agencies subject to the Common Rule, the VA recently received a copy of NBAC's report. It is my understanding that all Federal agencies responsible for conducting research will be reviewing our report fully and providing comments to the National Science and Technology Council by the end of May.

Mr. Chairman, the subject of this hearing comes at an important time in the history of human subjects' protections in this country. The opportunity exists to identify and correct deficiencies in the present system, but also to plan for how best to build the system, as we move into the next century. In NBAC's view, the enhanced protections recommended in its report will promote broad-based support for further research by engendering greater public trust and confidence that subjects' rights and interests are fully respected. I will be pleased to answer any questions you may have, and I apologize for going slightly over time.

[The prepared statement of Dr. Meslin appears on p. 129.]

Mr. EVERETT. That is quite all right. It does not make any difference if I am sitting in this chair or the gentlelady is sitting in this chair; we view this as a very serious matter. As a matter of fact, I believe you are basically aware of what has happened in west Los Angeles. While I am on the subject of west Los Angeles, the gentlelady will make a site visit out there, when her schedule permits, and also down to Tampa, along with other members.

You are aware of what happened to LA, and the suspension of research and the cases were researched without consent. How serious is this? Are we overacting?

Dr. MESLIN. Mr. Chairman, whenever you see a flaw in a system of protections, irrespective of whether there is a known identified harm that occurs, I think you should always take that very seriously. One does not have to wait for the bus to hit someone at a busy intersection to put up a stop sign.

Mr. EVERETT. I apologize, I had forgotten that the two other two witnesses will make statements. We will suspend with the questioning and we will begin with Dr. Shamoo.

TESTIMONY OF ADIL E. SHAMOO

Dr. SHAMOO. Thank you, Mr. Chairman. I am Adil E. Shamoo from Columbia, Maryland. I am a professor at the University of Maryland School of Medicine. I am here to speak on behalf of an advocacy group called Citizens for Responsible Care and Research. I have been advocating for greater protection for human subjects for the past 10 years, including I chaired the conference to discuss the NBAC's recent report.

Mr. Chairman, a man serves his country; he comes back with a disability, post-traumatic stress disorder, or with depression or even schizophrenia. He turns to his VA hospital, expecting care and compassion. His doctor is the one who can help him the most; his doctor is a psychiatrist. He treats him and he becomes stable and functional. His doctor, however, is also the researcher who conducts experiments on patients. His doctor asks him to sign an informed consent. The doctor then proceeds to take him off medication abruptly. This causes him to become psychotic. In some instances, he is left in the community with psychosis, delusion, depression, or post-traumatic stress disorder for weeks and months. Or the researcher might administer chemicals such as cocaine or amphetamine, or Yohimbine, an African drug, to induce psychosis or delusion or post-traumatic stress disorder, because he wants to study the illness. Is this fair?

Let me state also that we support ethical research with human subjects where basic human rights are fully respected, but we do strongly oppose unethical research.

The problem before us falls into one or more of the following categories; one, non-compliance with the existing Federal regulations; two, non-enforcement of the existing Federal regulations; three, no independent oversight and no accountability, and, four, the need for legislative reforms of the Federal regulation.

Let me give you an example I received just yesterday. It was not in my written statement, which is much longer. From the head of the IRB Committee, to all his investigators at University of Cincinnati, and those are the ones that deal with the VA hospital in Cincinnati: In his first sentence, he says, "It has become increasingly apparent that adverse events/death reports are not always being filed with the IRB in a timely manner, and in some instances not at all." That is deaths are not reported while on human subjects.

The following are the four categories of problems with research that have come into scrutiny and criticism. One, sudden medication

washout study. In these experiments, researchers take stable patients, many of whom are living in the community, off medication. As a consequence, most relapse into a psychotic state.

Two, chemical provocation experiment—that is called challenge study—in which patients are injected with chemicals of no therapeutic benefit, such as cocaine and amphetamine and ketamine, which is an animal tranquilizer, in order to provoke symptoms of psychotic episode.

Three, the fundamentals of informed consent are blatantly violated. Patients incapable of comprehending the purpose of research or the risks involved are asked to sign informed consents. Insufficient information to make an informed decision, and duress and coercion are commonplace.

And, four, hiding data on the number of suicides or attempted suicides enrolled in psychiatric research, although the incidence of suicide is very high in this population.

I have seen data, as you heard before, we do not categorize them as VA versus non-VA, but I was able to include, and it is in my written testimony, about eight cases, which involve VA, and yesterday I received another one. But, let me give you just a couple of them here.

One, a relapse experiment involved 88 veterans who had been stable and living in the community when they were recruited and hospitalized for 8 to 10 weeks. Their medication was abruptly withdrawn and replaced by a standard dose of Haldol. They were then washed out, subjected to lumbar puncture, and observed for at least 6 weeks, without medication, to see who will relapse. According to the investigators, 50 of these patients had been subjects in their earlier study; 30 have been used repeatedly in three separate experiments. Each involved lumbar puncture and abrupt withdrawal for all medication for 6 weeks to see who would relapse. In each experiment, about 50 percent relapsed.

Two, induction of post-traumatic stress syndrome on 26 veterans who were given Yohimbine to induce PTSD, and there are others, and others, and others.

In 1994, we complained to OPRR about an L-Dopa experiment conducted on 28 veterans at Bronx VA Medical Center, which is currently under investigation. These recovered veterans, while living in the community, were recruited into an experiment that was deliberately designed to induce psychotic relapse. All 28 veterans suffered the agony of psychotic relapse in order for the investigator to record how long it will take to relapse.

We call for the following national reforms: one, a moratorium on non-therapeutic high-risk experiments; two, enactment of a National Human Subject Protection Act that will cover, without regard to the source of funding, privately-funded or Federally-funded.

Currently, there is a National Animal Welfare Act. If you do an experiment on an animal, you must comply without regard to the source of funding, whether it is private or Federal. With humans that is not the case. Only Federally-funded research is covered by the Federal regulations. All private research is not covered by any Federal regulations, unless you are going to apply for a drug license.

Three, a prohibition on conducting above-minimal risk experiment on a vulnerable person.

Four, 51 percent of the Institutional Review Board should be independent scientists and community representatives not affiliated with the research institutions. Remember, IRB members are employees—the secretary, the nurse, or the doctor—of that same research institution.

Five, a comprehensive investigation either by the GAO or by the Justice Department of these past abuses.

Six, adverse events, just like adverse events that cause you to drop out of research, should be reported by a hotline to the FDA and OPRR.

And, seven, require a no-fault personal injury insurance of \$250,000, so that taxpayers do not have to pay the consequences of human subject abuses. It will be a no-fault insurance.

Thank you very much, Mr. Chairman.

[The prepared statement of Dr. Shamoo appears on p. 143.]

Mr. EVERETT. Thank you, Dr. Shamoo.

Dr. Paul Appelbaum.

TESTIMONY OF PAUL APPELBAUM

Dr. APPELBAUM. Mr. Chairman, I am Paul Appelbaum, M.D., testifying on behalf of the American Psychiatric Association. I am professor and Chair of the Department of Psychiatry at the University of Massachusetts Medical School, and I serve the APA as its vice president elect and Chair of its Ethics Appeals Board.

My writing over the last two decades has focused on the legal and ethical aspects of medical practice, including informed consent to medical research. The reported lapses and abuses at the West LA VA Medical Center are very serious and, in our view, in several cases unconscionable. The Federal Government and the American people owe a special debt of gratitude to our veterans, and we must ensure that they are protected when they receive medical treatment. I greatly appreciate the committee's interest in protecting the safety and rights of veterans participating in VA medical research.

In all medical research, the interests of patients should come first. In our pursuit of more effective treatments for individuals suffering from illness, researchers must never compromise the rights of patients. Subtly coercive techniques to obtain consent are unacceptable, as are inadequate disclosures of information to potential participants and failures to ensure that patients truly understand the consent documents they sign.

Simply put, if research cannot be performed without violating the rights of participants, it should not take place at all. As a society, we must be particularly careful to protect individuals participating in research whose illnesses may impair their decisionmaking ability; thus, reducing their capacity to protect themselves. In these cases, additional safeguards are required.

As the committee proceeds with its oversight hearings, I hope your efforts will include encouraging additional training and sensitization of investigators implementing additional verification that protections are, in fact, being used in high-risk subjects and creating additional protections in the informed consent process.

But, we must also respond after prudently reviewing the fact. We must carefully craft these protections so as not to unnecessarily impinge on the developments of new treatments of illness and disease. Only with research can we dramatically improve current treatment for patients and also develop medications for presently untreatable conditions.

Questions are periodically raised, as they have been here today, about studies involving discontinuation of medication or other treatment, unless commonly-used research techniques that may result exacerbation of patient's symptoms, so-called challenge studies. Such medication discontinuation and challenge studies occur throughout medicine and are not limited to a single discipline.

Why are these studies undertaken? These studies are performed for many reasons. Perhaps most importantly, these studies have played, and will continue to play, a critical role in developing many new medications that can transform and save patients' lives. It would be very difficult, if not impossible, to develop and ensure the safety of many new medications without the ability to take competent and informed patients off their current medications for some period of time.

Of course, these studies require major safeguards for patients. Investigators should bear the burden of demonstrating why the advancement of knowledge is significant enough to justify asking patients if they are willing to discontinue their medication. Moreover, both types of studies should exclude patients who are likely to suffer major distress or significant social, economic, or social consequences if their symptoms reappear or worsen.

Needless to say, patients should be told clearly about the possible consequences of stopping medication or participating in a challenge study and patients should be allowed to participate only if they provide a competent informed consent, and provisions should be made for close monitoring of patients who have discontinued their medication with clear criteria for the reinitiation of treatment if needed. By taking these and other steps, patients' rights and well-being can be protected.

It is an understandable first response to wonder whether individuals with a significant psychiatric diagnosis or any impaired decisionmaking from other causes should be participate in research. However, preventing or dramatically curtailing the participation of these people in research would be a tragic mistake. Much valuable research would be slowed or halted. If needed safeguards are taken—and I have outlined, some of those—such a drastic step is simply not needed to protect these individuals.

With special protections, such as testing, to ensure that individuals truly understand the implications of research participation, and allowing potential participants to discuss options with family members, the majority of patients with psychiatric disorders and even many patients with impaired decisionmaking can exercise informed consent.

It is also tempting, I know, to question whether research should be undertaken that does not produce a direct short-term benefit for research participants; that such an approach does not stand up to scrutiny. Such research is essential if we are to develop medications for many currently untreatable illnesses. It is also important

to remember that patients participating in this type of research at some point later in their lives, perhaps 15 or more years later, may dramatically benefit from a treatment breakthrough made possible by the research in which they participated.

All research involves risks. Generally, we allow competent patients to decide to run these risks after ensuring they have been well informed and appropriately protected, and that the study is likely lead to knowledge proportionate to the risk involved. These same principles should apply to all medical research, including the classes of study we have been discussing here today.

In conclusion, all of us must expand our efforts to prevent any lapses and abuses like those found at the West LA VA Healthcare Center from reoccurring. I believe and I hope the members of this committee will agree that the pursuit of new treatments for illness and the protection of the rights of research participants are not mutually incompatible goals.

I would like to thank you again for the opportunity to testify, and I look forward to working with you and your staff on these critical issues.

[The prepared statement of Dr. Appelbaum appears on p. 136.]

Mr. EVERETT. Thank you very much, Dr. Appelbaum. You mentioned earlier in your testimony that the research committee must be particularly careful to protect individuals participating in research whose illness may impair their decisionmaking ability; thus, reducing their capability to protect themselves. You mentioned in your written testimony that additional safeguards are required. Would you like to elaborate on those?

Dr. APPELBAUM. I would be happy to. The major concern in including such individuals in research is that, because of their limitations, they may not truly understand what they are getting into, and these concerns extend beyond psychiatric patients, to elderly patients, and sometimes to patients who are simply overwhelmed by their illness and confused by the circumstances in which they find themselves. And there have been allegations that at least one of the patients in the cardiology studies at the West LA VA Medical Center falls into this category.

In such circumstances, there are number of protections that could be required that one might want to implement sequentially, depending on the degree of risk that such patients face by entering into studies. For example, one might require investigators to use additional educational techniques with such subjects, and after such repeated exposure to information, rather than one-shot disclosures which are employed to test the understanding of subjects. So that, before they enter into the studies, you can be sure that they really do understand what they are getting into. Without such testing, it is completely uncertain whether subjects truly understand what they have heard and what they have agreed to.

Secondly, it may be important, particularly, again, in high-risk studies, where some assessment of patient decisionmaking capacity is to take place before they are given information and asked to consent to the studies, that testing can be done as part of routine procedures by the research team, which I think will be feasible in many circumstances. Or, again, particularly, in higher-risk studies, you might ask somebody outside the research team to undertake

such efforts. Those are examples of the kinds of protections that I was referring to.

Mr. EVERETT. Dr. Meslin, earlier, I asked you if we have been overacting, and I appreciate your answer. Do you believe the VA's response in their written testimony is adequate? Have you had a chance to review it?

Dr. MESLIN. I have heard the testimony and read it alongside with others here. NBAC has not reviewed the testimony to determine whether it is likely to solve the problems. I think it is fair to say the response that the VA has given is both timely and welcome, from Dr. Kizer's testimony, of responding as quickly as the VA did.

I think the most important point, though, Mr. Chairman, is whether or not the promise of procedural reform and remedy is likely to prevent the kinds of concerns and potential abuses that we have heard today. I applaud the VA for making the kinds of recommendations that they are making with respect to a new oversight panel. This is not unique to the VA. There are many other similar proposals that have been recommended in past years for quality assurance, accreditation, and, as NBAC has indicated in its report, for audit and disclosure. I think the test will be whether or not in time we can reduce the risk of such harms to as low a number as is feasibly possible, recognizing that you can never, as Dr. Appelbaum already indicated, reduce the risk in research to zero.

Mr. EVERETT. Ms. Brown.

Ms. BROWN. Thank you, Mr. Chairman. Let me say that this panel is just right on target as far as where they are.

Dr. Shamoo, I want to let you know that I think your comments were just right where I am as far as whether or not veterans just receiving medication—you know, I do not understand why you would withdraw it if they are elderly and they really need it, and I think your comments about are right on target.

I really have a concern about the number of homeless veterans, and I think one of the problems relates to those that have mental health problems, that in some way they have fallen through the cracks. My question is, this research, do you think it tends to push them back down hill, when they are working trying to get out of this situation? I mean, what do they get out of it? Or what do we get out of it?

Dr. SHAMOO. The one we are criticizing is not the minimal risk or, what is called, minor increment above minimal risk. We are talking about high-risk experiments where the patient could either attempt suicide or be needlessly in pain and suffering by these veterans. That is what we are really talking about. And the patient still has no benefit whatsoever from it. So this is the category; this is an extreme category.

So, yes, I think there are evidence now in the media and in our testimony—to NBAC, we brought a dozen families from all across the country. These patients have suffered brain damage, neurotoxicity, and there is psychiatric literature indicating that their social connections they made while they were well—they are all disconnected; they are losing their jobs. So, of course, there are damages, and this is only, in my view, the tip of the iceberg.

I stated in 1996 to the U.S. Senate Government Affairs Committee that this thing is going on in all medical centers and VA hospitals, and we have been talking about it for 7 or 8 years. Now, you are talking about tens of thousands of patients are enrolled in these high-risk experiments. These kinds of needless pain and suffering are occurring, and regression of these patients within their own recovery is happening as we speak now.

So, it is very unfortunate. I am not as sanguine as my colleague on the far right speaks that these are essential. I agree with all of his protective measures. However, these protective measures—none of it that I know of from the open literature has been complied with or there are currently ongoing—none of it.

Ms. BROWN. Will the other panelists respond to my question, please?

Dr. APPELBAUM. There is no question that nobody condones research that unnecessarily puts patients at risk, but it is important, I think, to focus on the fact that certain kinds of research techniques which may involve—for example, you asked a question earlier about taking a patient off medication. Let us assume that you have a new drug you want to test, whether it is for depression or hypertension or diabetes. In order to test the efficacy of that new drug, you have to, of necessity, stop the older drug that the patient has been taking, allow that drug to wash out of the patient's system, which may take days in some cases or a couple of weeks in others, and then start the new medication, to see whether it is as effective or more effective than the comparison drug. That kind of medication discontinuation and washout study is a bread-and-butter research technique. It is essential in order for new medications—

Mr. EVERETT. What if that patient has some kind of reaction to that withdrawal? That is acceptable in the scientific community?

Dr. APPELBAUM. Patients should never be placed in that situation if they have not given a competent informed consent, knowing what the potential risks are, and haven't voluntarily agreed to run those risks. That goes without saying. Nor should they be put in that situation if the potential consequences of discontinuing their medication are likely to be catastrophic.

But, I think, as we have recognized here today, that there are always risks associated with research, and we have generally allowed people to choose to run those risks for the sake of advancing knowledge in the field, and that is probably not a practice that should be shut down entirely. Rather, it is a practice that should be hedged with safeguards in order to make sure that patients are truly protected.

Ms. BROWN. What if this patient were put in this situation without that patient's knowledge?

Dr. APPELBAUM. That is unconscionable.

Ms. BROWN. Okay. Would you—

Dr. SHAMOO. Yes, may I respond? The current practices that he just mentioned—medication discontinuation, this is a nice word they have adopted recently after the patients and their advocates have been raising hell about it. They used to call it "washout," the good old name "washout." Now, they call this "medication discontinuation" because of the drug-free period.

If you take psychiatric patients, schizophrenic patients—let us take the extreme cases to illustrate the point—off medication suddenly, abruptly, like they have been doing all the time, the relapse rate—that is, full-blown symptoms—occurs somewhere between 50 to 80 percent of these patients. If you just simply taper it off, slow tapering it off, like you would do if you are taking care of the patient as a patient, not like a test tube, as a guinea pig, the relapse rate goes down to 15 to 20 percent. The current practice is abrupt.

The other point is that those patients are left in the community. You can take them as inpatients and they receive 24-hour care. So, in case they become psychotic and delusional or suicidal, then can be taken care of. That is not done now.

The other one is that I have not seen in the open literature, not a single case, where they—even Dr. Kizer mentioned this, that there were 400 schizophrenic patients who were psychotic and delusional. And about 200 they could not get an informed consent, and 100 surrogate, and 100 gave informed consent. That is not the case. What will we have in the literature? Four hundred schizophrenic patients who are psychotic and delusional and they all voluntarily signed informed consent. That is what it is now in practice.

Ms. BROWN. Can I have another minute? I want Dr. Meslin to follow up with some kind of response.

Dr. APPELBAUM. The techniques to which Professor Shamoo is referring, slow tapering of medications to diminish the effects of withdrawal, abrupt withdrawal of medication, close monitoring of patients, he talks about doing it at inpatient facilities. Often that will be appropriate. Sometimes patients can be monitored on an outpatient basis, as long as they are seen frequently enough. That may mean in appropriate cases several times a week, not just once a week. Those are good and appropriate measures that in many instances should be taken in order to protect subjects. I do not think we disagree about that at all.

Ms. BROWN. Dr. Meslin?

Dr. MESLIN. I think it is best to say, to indicate what the Commission had said on this issue, and it said I think two or three important things. The first is that, when one designs a study from the outset and thinks about the various types of methods that you are going to use, that is the first instance in which ethical issues should come to the attention to the investigator. Why this method, rather than another method? The Commission makes a recommendation regarding research design—I think I would include in the category of non-controversial.

A second way of thinking about this is asking whether patients fully understand what the nature of the discussion is. "Rapid" versus "slow," these can often be terms of art, and the Commission did not adjudicate between these scientific debates, but rather felt that the concern about rapid withdrawal, where there is an increased chance of harm, clearly falls in the category of ethically worrisome and ought not to occur.

Having said that, the Commission did not have an opinion about the volume of research that is occurring, and I think that is something that this subcommittee has been struggling with. We had to make a recommendation—it turns out to be recommendation 20 of

our 21 recommendations—that the Department of Health and Human Services contract with the Institute of Medicine to actually understand the nature and extent of some of these types of designs. So, there is an empirical question that is begging to be asked.

But, even if we knew what the amount was, the volume of research, that does not in any way obviate your obligation to think about those prior two questions: the ethics of research design and the ethics of informed consent.

Ms. BROWN. Thank you, Mr. Chairman, and let me say thank you for having this hearing today, and I will schedule my visits in the next couple of weeks. This is going to be on the top of my priorities because I think this is very important, and I think we need to follow up.

Mr. EVERETT. I appreciate the gentlelady's willingness to have site visits and her interest in this.

Well, it has been—I do not want to say “interesting”; it is worse than that—it has really been a serious matter of serious concern. And I said earlier, and I believe every word of it, it does not make a difference if I am sitting in this chair and the gentlelady sitting in this chair; we are going to pursue the VA and make sure that this does not happen again.

Dr. Shamoo, you read from a memo that was not included in your written testimony. If you would provide the subcommittee a copy of that—

Dr. SHAMOO. Absolutely. I will provide the entire document, yes, sir.

[The information follows:]

UNIVERSITY OF CINCINNATI MEDICAL CENTER,
INSTITUTIONAL REVIEW BOARD,
UNIVERSITY OF CINCINNATI,
Cincinnati, OH.

TO: All Clinical Investigators,
FROM: Harry Rudney, Ph.D.; Co-chairman,
University of Cincinnati Medical Center,
Institutional Review Board
DATE: December 4, 1998
RE: Adverse Event/Death Reports

It has become increasingly apparent that adverse event/death reports are not always being filed with the IRB in a timely manner, and in some instances not at all. Often, the accounts are received months after the occurrence, or are forwarded at the time of the annual progress report. In some cases, Section II of the progress report form lists deaths or adverse events as having occurred during the period of the report; however, when the IRB staff examines the file, there is no official previously submitted documentation to support these incidents. DHHS regulation 21 CFR 312.32 clearly states that all deaths and unanticipated or unexpected adverse reactions must be reported to the Chairperson of the IRB immediately and a written summary of the circumstances surrounding the adverse reaction or death be submitted to the IRB office within ten days of the occurrence. Because the IRB relies a great deal of the expertise of our investigators to assess the report of the adverse event, it is very important that you advise us concerning the relationship of the adverse event to the intervention, whether or not a change in protocol is necessary to minimize risks and whether or not information about the adverse event is germane to consent and/or re-consent/notification of subjects already enrolled is needed. While the IRB recognizes that the information about the adverse event may not be complete at the time of reporting, this should be reflected in your assessment. In order to facilitate IRB review of your adverse event and to avoid unnecessary

delays, please ensure that each applicable section of the AE report form (attached) is completed according to the instruction.

Perhaps a reminder as to the regulations would be in order. These are very clearly detailed on the reverse side of the UCMC adverse event report form as follows:

A serious adverse event means an adverse event occurring at any dose that results in any of the following outcomes: (1) death, (2) a life-threatening reaction (one that places the subject/patient, in the view of the investigator, at immediate risk of death), (3) a persistent or significant disability/incapacity; (substantial disruption of one's ability to conduct normal life functions), (4) hospitalization or extension of an existing hospitalization; (5) a congenital anomaly (birth defect in offspring of subject taking the product, regardless to time to diagnosis, or (6) any medical event which requires treatment to prevent one of the medical outcomes listed above.

Compliance with these regulations is extremely important to insure that the University of Cincinnati Medical Center maintains accurate records and follows the regulations of the FDA and the Office of Protection of Research Risks (OPRR) in this regard.

Mr. EVERETT. I want to thank my colleagues for their participation in this hearing and our witnesses for their testimony.

I think it is quite clear that the VA must establish a system for ensuring accountability and informed consent and other aspects of research programs. The VA is responsible for the programs and for protecting our veterans, not a watchdog for NIH. The Department has failed miserably in doing a job in west Los Angeles. I am glad to hear the VA has now planned to set up an office for research compliance to begin external accreditation. Other VA facilities are going to be investigated. We do not know what will be found, but we do request both the OPRR and the VA keep us informed of progress and report to us when investigations are complete.

It is also quite apparent that the VA cannot offer the subcommittee satisfactory assurances that these problems we have heard about today do not exist in other VA research facilities. Therefore, the subcommittee will ask for an independent audit to go over VA research facilities with a fine-tooth comb and report back to us in approximately 6 months. If in the interim, informed consent or other problems are found, we will ask that they be coordinated immediately with the appropriate Federal agencies, such as OPRR or FDA.

Now, speaking for myself, I would like to see the VA medical research bounce back from this strong, to be strong and vital, but I can promise you that if I ever hear again of medical research without veterans' consent at a VA facility, I will do my dead-level best to put that facility out of the research business permanently, whether it is West LA or any place else.

The members will have five legislative days to submit their statements and written requests for the record. I appreciate this panel and all panels for their participation today.

The hearing is adjourned.

[Whereupon, at 2:35 p.m., the subcommittee was adjourned.]

APPENDIX

PREPARED STATEMENT OF CHAIRMAN EVERETT

The hearing will come to order.

Good morning! This hearing will examine the suspension on March 22, 1999, of all medical research at the West Los Angeles and Sepulveda VA medical facilities. It will also examine informed consent issues in VA medical research generally. After learning of the suspension of the research, Chairman Cliff Stearns of the Health Subcommittee, and Ranking Democratic Member Corrine Brown of the Oversight and Investigations Subcommittee and I were extremely concerned and decided to have an expedited joint hearing. We wanted a public report on what happened and what is being done about the situation. Obviously, the VA has failed to protect our veterans at the West Los Angeles medical research facility. We know that much already.

The Subcommittee on Oversight and Investigations has been conducting oversight of VA patient safety issues as part of its oversight plan and I regard this as a major patient safety issue.

This is the most serious trouble in VA medical research in many, many years. For the VA, the suspension is unprecedented. VA medical research is too important not to do it right. It has given veterans and all Americans many pioneering advances in medicine. We insist that the VA find out what the problems are and correct them. We also insist that those who are responsible be identified and held fully accountable, something that the VA has not been consistent in doing.

The issues before us today revolve around veterans giving informed consent before participating in medical research. Without informed consent, no veteran can properly be a research subject. The concerns about informed consent go straight back to the awful things the Nazis did to people during the holocaust and called it medical research. The civilized world vowed that it should not happen again and in 1949 made a statement known as the Nuremberg Code to establish ethical guidelines for human medical research.

I'm deeply disturbed and I'm appalled by the reports that four veterans at the West Los Angeles VA were the victims of medical research without any consent whatsoever. One of the veterans even refused consent.

These veterans, who will not be publicly identified, were old and sick, and three out of four had psychiatric conditions—they were particularly vulnerable and a VA doctor took advantage of them. Their faces are the faces of veterans in VA hospitals across the country. The subcommittees demand an explanation and accountability. These outrageous crimes against our veterans must not happen again.

Our witnesses today are from the HHS Office for Protection from Research Risks, from the VA's Washington office and from the West Los Angeles VA. Also, we have a panel of experts in medical research ethics to give us their evaluations.

Two organizations, The American Legion and the National Alliance for the Mentally Ill, have submitted written statements for the record.

At this time, I'll recognize the distinguished Chairman of the Subcommittee on Health, Mr. Stearns.

CHAIRMAN'S CLOSING STATEMENT

I thank my colleagues for their participation in this hearing and our witnesses for their testimony. I think it is quite clear that the VA must establish a system for ensuring accountability in informed consent and other aspects of its research programs. The VA is responsible for the programs and for protecting our veterans, not a watchdog office at NIH. The department has failed miserably in doing its job in West Los Angeles. I'm glad to hear that VA is now planning to set up an office for research compliance and to begin external accreditation.

Other VA facilities are going to be investigated. We don't know what will be found, but we do request that both the OPRR and the VA keep us informed of progress and report to us when the investigations are completed.

It is also quite apparent that the VA cannot offer the Subcommittees satisfactory assurances that these problems we have heard about today do not exist at other VA research facilities. Therefore, the subcommittees will ask for an independent audit to go over VA research facilities with a fine toothed comb and report back to us in approximately six months. If in the interim, any informed consent or other problems, are found we will ask that they be coordinated immediately with the appropriate federal agencies, such as OPRR or FDA.

Now, speaking for myself, I would like to see VA medical research bounce back from this strong and vital. But I can promise that if I ever hear again of medical research without a veteran's consent at a VA facility, I will do my level best to put that facility out of the research business permanently, whether it's West LA or anywhere else.

PREPARED STATEMENT OF HON. LUIS V. GUTIERREZ

Thank you, Mr. Chairman. I would like to thank the witnesses for being here today. I hope that this hearing will give us the opportunity to find out what transpired at the Veterans Affairs medical center in West Los Angeles and Sepulveda. I am deeply disturbed at the reports of veterans being exploited by staff at VA hospitals for research purposes. These are very serious allegations which suggest that doctors put aside their consciences and medical responsibilities to achieve personal gain.

Thousands of veterans in this country rely on the VA for medical care and treatment. I recognize that many important medical advances have come from VA medical research. Many veterans welcome the opportunity to participate in medical research programs that offer them the most advanced treatment available. But if informed consent requirements for veteran patients are not respected and researchers are not held accountable for their unethical research practices, VA research should not continue.

Much to my dismay, I believe that the VA is in crisis and that the problems identified at West Los Angeles and Sepulveda reflect larger problems. As we know, the Department of Veterans Affairs is facing severe budget constraints. The lack of proper funding has led to the reduction in medical staff at VA hospitals by the thousands. It is not uncommon for a veteran to wait months to see a doctor for an examination. I also understand that some VA hospital administrators are receiving bonuses for eliminating nurses, physician assistants and other medical staff because they are "cutting costs." I am very concerned that the severe budget crisis the VA is facing is responsible for creating a system where mistakes, abuse and consistent inadequate care is the norm for our veterans.

In this specific case, if we find that patients were in fact used for research purposes by their doctors without consent or in violation of strict medical regulations, we must hold those doctors accountable. We must also make every effort to ensure that if illegal and unethical violations were committed by medical staff, such crimes must never occur again at any VA facility.

But the work must not stop there. Patient care should be our most important priority.

Mr. Chairman, the VA has many doctors and nurses who are dedicated to their jobs and the patients they serve. Perhaps these men and women do not receive the recognition they deserve. However, this specific case should serve as a wake-up call for the entire system. Our VA health care system is failing our veterans. More money, more programs, more oversight and more dedication to our veterans is desperately needed.

CBS NEWS

Number 528

524 West 57th Street, New York, N.Y. 10019



April 15, 1999

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CBS NEWS

48 HOURS

April 15, 1999

DAN RATHER: *(Voiceover)* 48 HOURS, we take you there.

(Footage of Shalmah Prince; ambulance; hospital)

Announcer: *(Voiceover)* When Shalmah Prince got sick, she went to the hospital to be treated.

Ms. SHALMAH PRINCE: It was frightening.

(Footage of hospital; Shalmah)

Announcer: *(Voiceover)* But instead, they experimented on her.

Mr. GASTON COGSDELL: We trusted the doctor.

Ms. PRINCE: Did they tell me any of the risk? No.

(Footage of Shalmah; documents)

Announcer: *(Voiceover)* She says her life was ruined.

Ms. PRINCE: To me, experiments were something the Nazis did.

(Footage of Santana family in cemetery; photo of Joseph Santana; Maria Santana and Erin Moriarty; documents; gravestone)

Announcer: *(Voiceover)* And the Santanas say what happened to their brother was even worse. Erin Moriarty investigates. Did he take the ultimate risk without even knowing it?

Ms. MARIA SANTANA: They are responsible for my brother's death.

(Footage of Susan Spencer and David McLoughlin with paperwork; close-up of paperwork with text highlighted: 2,280,000 present balance; video still of Bruce Diamond; photo of Richard Borison; machine with pills; person counting money)

Announcer: *(Voiceover)* Plus...

SUSAN SPENCER: *(Voiceover)* What is this \$2.28 million?

Mr. DAVID McLOUGHLIN: *(Voiceover)* Checking account.

Announcer: *(Voiceover)* These two doctors got rich by running phony drug experiments.

Dr. BRUCE DIAMOND: It was almost like an addiction to see how much you can make.

(Footage of artwork at auction; photo of Borison; blueprint of castle)

Announcer: *(Voiceover)* How rich? He was building a castle.

Mr. McLOUGHLIN: It was gonna have a moat.

(Footage of blood pressure measuring device; Bill and Marion Hatcher)

Announcer: *(Voiceover)* Their patients paid a high price for their high living.

SPENCER: And you trusted them?

Mr. BILL HATCHER: One hundred percent.

(Footage of Spencer; Diamond in prison; cell door being closed; Alain Lareau; syringe; documents)

Announcer: *(Voiceover)* Susan Spencer reports they almost got away with it. And this homeless man has been in more than 10 drug studies.

Mr. ALAIN LAREAU: There's no other way you can go out and work and make that kind of money that fast.

(Footage of document; Lareau; Troy Roberts; pills; sign: Experiment in progress; medical equipment; photo of Joseph Santana; footage of Shalmah)

Announcer: *(Voiceover)* So what could be wrong with that? Troy Roberts has the story. Shocking abuse in human testing. Ultimate Risk.

(48 HOURS opening footage)

WIRED

ERIN MORIARTY: What does it take to get all these drug remedies to your pharmacy? You may be surprised and disturbed by some of the sacrifices that are being made for the sake of medical progress.

Good evening. I'm Erin Moriarty. Dan Rather's on assignment. The benefits of all these medicines and treatments are indisputable. But there's growing evidence that the people being used in vital research to develop all these drugs could be at risk, even the ultimate risk. 48 HOURS conducted a six-month investigation of questionable practices in human testing. Tonight, we'll document cases of dangerous abuse, hospitals doing experiments on patients who thought they'd be getting treatment. And then there's the money, lucrative drug company payments that can tempt some corrupt doctors into putting the most vulnerable among us at risk. We begin tonight with Peter Van Sant and one desperate volunteer who claims he never knew what he was walking into.

Unidentified Man #1: You got it OK? You ready?

Mr. DAN KEMP: Yeah, I'm ready.

Man #1: OK.

(Footage of Dan Kemp standing with help of two men)

PETER VAN SANT: *(Voiceover)* It looked like a medical miracle: paralyzed people standing on their own two legs...

Mr. KEMP: Ooh.

Unidentified Man #2: How does it feel, Dan?

Mr. KEMP: Ooh, feels vertical.

(Vintage footage of Sam Khawam walking up stairs; Peter Van Sant and Sam watching footage)

VAN SANT: *(Voiceover)* ...and then doing the unimaginable, walking, even climbing stairs.

A paralyzed man is walking on his own two feet. It's—it's amazing.

Mr. SAM KHAWAM: It is.

(Photos of Sam; vintage footage of Sam walking down stairs; Sam walking; footage of Veterans Administration Medical Center)

VAN SANT: *(Voiceover)* Sam Khawam was a 22-year-old with a promising engineering career when he was left paralyzed by a stray bullet. Several months after his accident, he became one of the first volunteers in an experimental functional electrical stimulation program, FES.

Mr. KHAWAM: *(Voiceover)* It was like the step on the moon.

VAN SANT: *(Voiceover)* It's a study that began in 1982 at the Cleveland Veterans Administration hospital with the hopes of creating artificial walking for paralyzed people.

Mr. KHAWAM: *(Voiceover)* You hear that there was no hope for you. And to see that working for me then was—was remarkable.

Dr. E. BYRON MARSOLAIS: *(From vintage footage)* We have proven feasibility.

(Footage of E. Byron Marsolais; vintage footage of Sam on stairs)

VAN SANT: *(Voiceover)* The lead physician of the project, the man who put Sam back on his feet, is Dr. E. Byron Marsolais.

Dr. MARSOLAIS: *(From vintage footage)* That's the muscle that we want. It goes right down here into the femur.

(Vintage footage of Marsolais demonstrating functional electronic stimulation; Sam; photo of Marsolais, woman and Sam; vintage footage of Sam standing in front of crowd)

VAN SANT: *(Voiceover)* Dr. Marsolais implanted thin steel wires in the leg muscles of volunteers and then sent electricity through the wires, causing paralyzed muscles to move.

Mr. KHAWAM: *(Voiceover)* We were going to walk again, so we—you know, we trusted him.

VAN SANT: *(Voiceover)* Dr. Marsolais took his artificial walking subjects on the road, and Sam was his biggest star.

Sam Khawam is now back in his wheelchair, unable to take a single step. And he claims that the wires which gave life to his paralyzed legs now threaten his life. Sam and several others among the 63 people who volunteered for the FES program at this hospital now claim they weren't properly warned that the implanted wires could be hazardous to their health.

Mr. KHAWAM: Now I would've never, ever joined that program had I known that I would ever even come close to these kind of infections.

Surgeries like from there—had two surgeries there.

VAN SANT: So these are all related to infections.

(Footage of Sam showing locations of surgeries in legs)

VAN SANT: *(Voiceover)* Since leaving the program in 1988, Sam says he's had 13 surgeries for recurring infections in his lower body that he claims are caused by more than 200 wires left behind by researchers.

How serious are they?

(Footage of Dudley Giles, Sam and Van Sant)

VAN SANT: *(Voiceover)* Dr. Dudley Giles of Meadville, Pennsylvania, has been treating Sam's infections for two years.

Dr. DUDLEY GILES: That was a wound that Sam had on his buttock area. There's probably a cavity a little bit larger than a softball on the inside.

VAN SANT: And inside that cavity you found wires?

Dr. GILES: At the base of them, there was wires, yeah.

(Photo of corroded wires)

Mr. KHAWAM: *(Voiceover)* The wire's getting corroded inside.

VAN SANT: *(Voiceover)* Dr. Giles is convinced these infections are being caused by the hundreds of wire fragments left in Sam's legs.

Dr. GILES: This is an X-ray of Sam's lower leg.

(Footage of X-ray; X-ray with wires highlighted)

VAN SANT: *(Voiceover)* We enhanced the X-rays to make the wires easier to see.

A layman—you'd almost think—'cause it's so extensive, you'd think these were blood vessels or something. These are all wires?

Dr. GILES: Those are all little wires, yeah.

(Footage of X-ray; Giles, Sam and Van Sant)

VAN SANT: *(Voiceover)* And Dr. Giles says the only way to remove all the wires would be to cut off all of Sam's muscle tissue or amputate his legs. Dr. Giles believes Sam faces a lifetime of infections, infections so severe, they could kill Sam if left undetected.

LEANNE: I can't deal with it. It—it upsets me every single time.

(Footage of Leanne and Sam)

VAN SANT: *(Voiceover)* Leanne is Sam's wife, and she's also a doctor.

LEANNE: I haven't been able to even help with his dressing changes 'cause it upsets me so much. And it's not like I've never done dressing changes before. I do them on patients all the time. But in my husband, and because of how it happened, it is just devastating to me.

(Footage of Sam in wheelchair; Sam getting into car and driving)

VAN SANT: *(Voiceover)* Sam sued the VA, which paid him \$80,000 in a settlement. And there are two other patients with similar infections who have also sued.

Some of the people we have spoken to today feel as though they were treated like guinea pigs. What about that?

Dr. JOHN FUESSNER: We treat all our patients like human beings.

(Footage of John Fuessner; building; sign: Department of Veterans Affairs; vintage footage of Marsolais)

VAN SANT: *(Voiceover)* Dr. John Fuessner is the chief research officer for the Department of Veterans Affairs. He was provided as a spokesman for the walking project after Dr. Marsolais declined repeated requests to talk with us.

Dr. FUESSNER: If there are adverse effects, that's part of the research, and I think that the benefits and the number of patients who have benefit far outweigh those that have not.

Mr. KHAWAM: I mean, for God's sake, you don't do this in dogs and cats. *(Footage of Sam and Van Sant; informed consent document with excerpt highlighted: Non-functional electrodes will be removed.)*

VAN SANT: *(Voiceover)* What angers Sam is what he says was a broken promise from the researchers. The 1982 informed consent that he signed said, 'All non-functional electrodes,' which are the wires, 'will be removed.'

Nowhere in this consent form does it make reference to the—the fact that hundreds of wires may be left in their legs as a result of this procedure.

Dr. FUESSNER: Well, again, that's a sensitive issue, and you know—and you know that's a sensitive issue. And I—I really can't comment specifically...

(Footage of Fuessner; Sam; vintage footage of Sam)

VAN SANT: *(Voiceover)* Because of pending litigation, VA attorneys limited what Dr. Fuessner could say. Sam has filed another lawsuit against other parties involved in the study. But in court documents, the government claims that there is no objective evidence that the remaining wire fragments are causing Sam's infections.

Mr. KEMP: I knew that there was gonna be foreign bodies implanted into—into my body.

(Footage of Dan)

VAN SANT: *(Voiceover)* Dan Kemp of Traverse City, Michigan, was in the same experiment and has been infection-free. Dan says he knew the risks.

Mr. KEMP: I knew that, with anything like that, that you run the risk of infection, maybe even death.

(Vintage footage of surgical implanting of wires)

VAN SANT: *(Voiceover)* But Dan only had 20 wires inserted in his legs, not the hundreds of wires Sam had implanted.

LEANNE: *(Voiceover)* It's sort of like the guy who made the Frankenstein monster.

You know, I'm beyond the science and what's required of me and what's required of every physician.

(Footage of Sam, Leanne and children playing in snow)

VAN SANT: *(Voiceover)* Sam and Leanne are concerned that the VA is still funding Dr. Marsolais' work. But they've gotten on with their life with their three children.

Mr. KHAWAM: Ooh. You missed.

(Footage of Sam, Leanne and children playing in snow)

VAN SANT: *(Voiceover)* And although Sam says he will never again volunteer for a medical experiment, he still dreams of the day he can walk again.

Mr. KHAWAM: *(Voiceover)* I'm hoping for a cure. I'm not obsessed about it.

I'm not stopping my life until it happens. But once it happen, I'll be very happy.

(Footage of Sam, Leanne and children; prison)

Announcer: *(Voiceover)* Coming up...

Dr. BRUCE DIAMOND: But I liked the money.

(Footage of Bruce Diamond; photo of Richard Borison; footage of document; model of castle)

Announcer: *(Voiceover)* ...these two doctors made a fortune.

SUSAN SPENCER: *(Voiceover)* \$2.28 million. That's healthy.

Announcer: *(Voiceover)* One of them was even building a castle...

Mr. DAVID McLOUGHLIN: It was gonna have a moat.

(Footage of Bill and Marion Hatcher)

Announcer: *(Voiceover)* ...at the expense of their patients.

Unidentified Reporter: Do you have anything to say to your patients?

(Footage of blood pressure measuring device; portfolio; cell door closing)

Announcer: *(Voiceover)* They almost got away with it. Next.

(Announcements)

DRUG MONEY

(Excerpt from auction)

(Footage of sculptures; auction)

SUSAN SPENCER: *(Voiceover)* Excited bargain hunters packed the hall in Augusta, Georgia, last December...

Unidentified Auctioneer: Sold, \$800.

(Footage of suits of armor)

SPENCER: *(Voiceover)* ...for one of the weirdest auctions of all time.

Auctioneer: Lot number 225 is all the swords and daggers and hatchets.

Unidentified Bidder: This is totally bizarre.

(Footage of artwork at auction; suits of armor)

SPENCER: *(Voiceover)* On the block, everything from antiques and paintings to suits of armor...

Auctioneer: So it's the one in the box.

(Footage of auction)

SPENCER: *(Voiceover)* ...worth a fortune.

Auctioneer: I have \$2,000, \$2,100, \$2,100, two—two—two...

(Footage of auction)

SPENCER: *(Voiceover)* It all belonged to the town's most famous and infamous doctors...

(Excerpt from auction)

(Photo of Richard Borison; video still of Bruce Diamond; artwork at auction; auctioneer; prison; Diamond in prison)

SPENCER: *(Voiceover)* ...Richard Borison and Bruce Diamond. They no longer need this old stuff. It doesn't work with their new decor. Pharmacologist Bruce Diamond, a PhD, convicted on 53 counts, including practicing medicine without a license and prescription fraud.

Dr. BRUCE DIAMOND: But I liked the money. It was almost like an addiction to see how much you can make. It was just a game.

(Footage of Diamond; photo of Borison; footage of pills; machine with pills)

SPENCER: *(Voiceover)* Over eight years, he and his partner, psychiatrist Dr. Borison, raked in more than \$11 million turning human drug trials into their personal money machine.

Dr. DIAMOND: It grew up to a few hundred thousand. Then it grew to millions.

(Photo of man with bottles of pills; sign: Medical College of Georgia)

SPENCER: *(Voiceover)* They pretended to be doing trials for the Medical College of Georgia, where they both were on staff, but they kept payments meant for the college for themselves.

Unidentified Reporter: Did you do it, Doctor? Do you have anything to say to your patients?

(Footage of pills with graphics on screen: Zeneca, Otsuka, Sandoz, SmithKline Beecham; Abbott; Parke-Davis; footage of patient being injected; heart monitor; IV drip)

SPENCER: *(Voiceover)* And in the process, they deceived some of the top drug companies in the country, to say nothing of the patients they put at risk.

But still, how could they possibly make \$11 million? Easy. Drug companies pay doctors enormous amounts to do drug trials, sometimes as much as \$20,000 per patient in a study. It's a system that invites corruption.

Dr. DIAMOND: I know that a lot of doctors are getting into it, probably ones that aren't even competent in doing research.

SPENCER: Just for the money.

Dr. DIAMOND: Right. Just for the money.

(Excerpt from auction)

(Footage of Bill Hatcher at auction; auctioneer)

SPENCER: *(Voiceover)* Bill Hatcher said he had to come to the auction just to see how they'd spent it all.

(Excerpt from auction)

(Photo of Bill and Marian Hatcher)

SPENCER: *(Voiceover)* Marian, Hatcher's wife of 52 years, was in one of the doctor's trials.

Mr. BILL HATCHER: No shaking.

(Footage of Bill and Marian)

SPENCER: *(Voiceover)* She has Alzheimer's.

Mr. HATCHER: When you discover that your wife or spouse or your loved one has this disease, you become very, very desperate.

I love you.

(Footage of newspaper ad; Bill and Marian Hatcher)

SPENCER: *(Voiceover)* That's when Hatcher saw an ad for Alzheimer's patients to test an experimental drug designed to slow the disease.

And it was your understanding from the very beginning that this study was being supervised by the Medical College of Georgia?

Mr. HATCHER: No ifs, ands or buts.

(Footage of newspaper ad with excerpt highlighted: The Medical College of Georgia is looking for 60; videotape footage of Marian Hatcher in clinic)

Mr. HATCHER: I mean, it was plainly in the paper.

SPENCER: *(Voiceover)* The lie was even caught on tape in video the clinic shot to record Marian's progress.

Dr. RICHARD BORISON: *(From videotape)* Do you know where we are and what we're called?

Mrs. MARIAN HATCHER: *(From videotape)* I don't know what you're called.

Dr. BORISON: *(From videotape)* The Medical—the Medical College of Georgia.

(Footage of Bill Hatcher; Bill and Marian Hatcher; footage and video still of Borison)

SPENCER: *(Voiceover)* And Hatcher says though these trials involved powerful drugs, no doctor oversaw Marian's care. And she was getting worse. So where was Dr. Borison?

Mr. HATCHER: I met Dr. Borison the—the day I withdrew my wife from the program, which was one and a half years later.

SPENCER: You didn't meet the guy who was supposedly...

Mr. HATCHER: I ne—never—never saw him.

Unidentified Child: *(Singing)* Happy birthday to you.

(Footage of child, Janis Huckeba and Lewis; photo of Lewis)

SPENCER: *(Voiceover)* Janis Huckeba never saw Dr. Borison, either. Her husband Lewis also was in the Alzheimer's study. One day, he became violent and psychotic.

Mrs. JANIS HUCKEBA: He got a gun and was sitting out on the patio, and he was going to blow the brains out of a family member.

(Photo of Janis and Lewis)

SPENCER: *(Voiceover)* Panicked, she called the clinic.

Mrs. HUCKEBA: Dr. Diamond is the one who was there.

SPENCER: But Dr. Diamond's not a medical doctor.

Mrs. HUCKEBA: That's true. Dr. Diamond wrote a prescription for my husband and signed it.

SPENCER: Did you know at the time that Dr. Diamond was a PhD but not a medical doctor?

Mrs. HUCKEBA: Nope.

(Footage of Diamond)

SPENCER: *(Voiceover)* And Bruce Diamond, PhD, wasn't correcting anyone's impression. After all, of the staffers who saw patients, he did have the best credentials.

Do you have a medical background?

Ms. ANGELA TOUHEY: I—I do not.

(Footage of Angela Touhey with Spencer)

SPENCER: *(Voiceover)* Angela Touhey was just two years out of college.

You were dosing patients?

Ms. TOUHEY: Well, I guess it sounds worse than—than how I saw it at the time.

(Footage of Angela with Spencer)

SPENCER: *(Voiceover)* But she was the research coordinator in charge of depressed and schizophrenic patients.

Ms. TOUHEY: I determined whether they needed to go up a dose or stay at that dose, if they needed to go—go back. And looking back, I mean, I just think, you know, who did I think I was that I could do that kind of thing?

(Footage of Angela with Spencer)

SPENCER: *(Voiceover)* She tried explaining her concerns to the doctors.

Ms. TOUHEY: Dr. Diamond said, 'We don't care how these patients are doing. We want to know how many patients you recruited in the past week.'

(Footage of Diamond in prison; copies of checks from Otsuka America Pharmaceutical; David McLoughlin; photo of Borison)

SPENCER: *(Voiceover)* Dr. Diamond says he remembers no such thing. But he doesn't deny that volume was key to keeping the money rolling in.

(Voiceover) \$75,000.

Mr. DAVID McLOUGHLIN: *(Voiceover)* \$75,000.

SPENCER: *(Voiceover)* \$160,000.

Mr. McLOUGHLIN: *(Voiceover)* \$160,000

SPENCER: *(Voiceover)* It came in so fast, prosecutor David McLoughlin says that Dr. Borison had trouble dealing with it all.

Mr. McLOUGHLIN: And—and we talked to the tellers. And he would come through the drive-thru and he would deposit it...

SPENCER: Through the drive-thru?

Mr. McLOUGHLIN: ...through the drive-thru and deposit six or seven multithousand-dollar checks every day.

SPENCER: Now what is this? \$2.28 million, present balance.

Mr. McLOUGHLIN: Checking account.

SPENCER: That's healthy. I didn't know banks would take checking accounts at \$2 million.

Mr. McLOUGHLIN: Banks love checking accounts that are this big.

(Footage of items at auction)

SPENCER: *(Voiceover)* It took a hefty chunk of the drug money...

(Excerpt from auction)

(Footage of items at auction)

SPENCER: *(Voiceover)* ...to buy all the antiques, art and armor. But the doctor had big plans.

Dr. Borison clearly felt a man's home should be his castle. And a castle was exactly what he had in mind. This is the architect's model of the 11,000-square-foot castle that he planned to build just outside Augusta.

Mr. McLOUGHLIN: This is Borison's pride and joy.

And this castle was gonna have medieval pennants hanging from it.

(Footage of blueprint of castle)

SPENCER: *(Voiceover)* Meeting room.

Mr. McLOUGHLIN: It was gonna have chandeliers hanging from turrets.

(Footage of blueprint of castle)

SPENCER: *(Voiceover)* Trophy room.

Mr. McLOUGHLIN: It was gonna have a moat.

(Footage of blueprint of castle; Spencer examining blueprint)

SPENCER: *(Voiceover)* Elevator.

(Voiceover) And it might have been built...

It's like a cathedral.

(Footage of Angela at auction)

SPENCER: *(Voiceover)* ...but for Angela Touhey.

(Excerpt from auction)

(Footage of auction)

SPENCER: *(Voiceover)* Desperately worried that patients were at risk, she blew the whistle.

(Excerpt from auction)

(Footage of items at auction)

SPENCER: *(Voiceover)* But if she hadn't...

Mr. McLOUGHLIN: They probably could've gotten away with it.

SPENCER: But how did they get away with it as long as they did? Who is watching doctors to be sure that drug trials are run properly and that patients are protected? The short answer is: no one.

Mr. GEORGE GROB: A lot of people are gonna be hearing about the study...

(Footage of George Grob; Department of Health and Human Services plaque)

SPENCER: *(Voiceover)* George Grob is the deputy inspector general for the US Department of Health and Human Services.

Does this system give the patient any safeguards?

Mr. GROB: Yeah, if the—if the doctor's not acting in good faith, I'd say the patient's at risk.

(Footage of Grob with Spencer; heart monitor; medical equipment; blood pressure measuring device)

SPENCER: *(Voiceover)* The supposed watchdog in the system is what's called the Institutional Review Board, independent organizations set up to approve and oversee drug trials. But they often oversee just on paper.

Mr. GROB: I think it's probably one of the crucial weaknesses of the current system.

(Footage of Diamond with Spencer)

SPENCER: *(Voiceover)* There is no requirement for any hands-on inspection.

Dr. DIAMOND: I mean, if you want to know, did they come out and visit us? Once in 10 years.

SPENCER: Once in 10 years?

Dr. DIAMOND: Yes.

SPENCER: These are the people that are supposedly monitoring this.

Dr. DIAMOND: They monitor us quarterly by paperwork.

SPENCER: Oh, great.

(Footage of Diamond; interior of prison; photo of Borison; footage of prison exterior; mug shot of Borison; footage of prison security equipment)

SPENCER: *(Voiceover)* About the only thing to discourage a doctor bent on fraud may be what happens if you get caught. Dr. Borison, the mastermind, is serving 15 years in a maximum security prison. He refused to speak to us. Dr. Diamond is serving five years and it's apparently changed him.

Dr. DIAMOND: I'd like to say at this point that who's ever watching and whoever I hurt in this process, I'm sorry for that.

(Footage of Diamond)

Dr. DIAMOND: (*Voiceover*) The last 14 months in prison, I've been repenting.

I know what I did was wrong. And I'm really sorry.

(*Footage of cell door closing; Shalmah Prince painting*)

Announcer: (*Voiceover*) Next....

Ms. SHALMAH PRINCE: I am a human being.

(*Footage of Shalmah painting; hospital*)

Announcer: (*Voiceover*) ...when she got sick, she went to the hospital to be treated.

Mrs. JENELLE COGSDELL: She's had a bad deal.

(*Photo of Shalmah; hospital*)

Announcer: (*Voiceover*) But instead, doctors experimented on her.

Ms. PRINCE: Did they tell me any of the risk? No.

(*Footage of painting; Shalmah*)

Announcer: (*Voiceover*) She says she's never been the same.

Ms. PRINCE: (*Voiceover*) It hits you at the deepest level.

Announcer: (*Voiceover*) Just ahead.

(*Announcements*)

HERE TO HELP?

(*Footage of Shalmah Prince painting*)

Ms. SHALMAH PRINCE: I am a human being, you know?

(*Footage of Shalmah painting*)

Ms. PRINCE: (*Voiceover*) I'm a human being. I was in a unit with 10 other people. We were all subjects in a study.

We all lost our face. And we all lost our identity.

(*Footage of Shalmah painting; Jenelle and Gaston Cogsdell*)

ERIN MORIARTY: (*Voiceover*) Shalmah Prince says what happened to her in a Cincinnati hospital turned her into someone even her mother has trouble recognizing.

Mrs. JENELLE COGSDELL: She's had a bad deal, you know. It—it has changed her. And—and life is not as pleasurable as it was.

(*Footage of Jenelle and Gaston; photos of Shalmah*)

MORIARTY: (*Voiceover*) Jenelle and Gaston Cogsdell's daughter...

This is Shalmah here?

(*Photos of Shalmah as child*)

Mrs. COGSDELL: (*Voiceover*) Mm-hmm, Shalmah when she was a three-year-old.

MORIARTY: (*Voiceover*) ...once a bubbly cheerleader and promising painter...

Mrs. COGSDELL: You can see all these pictures, every one of them. You know, she was everybody's favorite.

(Footage of Shalmah driving; key chain)

MORIARTY: *(Voiceover)* ...now she spends much of her day alone in her car...

Ms. PRINCE: There's a certain path that I take around town.

(Footage of Shalmah driving; bridge as seen from moving vehicle)

MORIARTY: *(Voiceover)* ...driving the same streets in her hometown of Cincinnati over and over again.

Ms. PRINCE: Well, I do have a course that I take when I start feeling like I need to get grounded.

(Footage of Shalmah driving)

MORIARTY: *(Voiceover)* She's been trying to find her way since one night, 15 years ago.

Ms. PRINCE: It was there.

MORIARTY: Was it the entire floor?

Ms. PRINCE: Yeah. It was the entire floor.

(Footage of hospital; Shalmah with Moriarty)

MORIARTY: *(Voiceover)* Shalmah, who had been suffering from manic depression for two years, had gone to the emergency room at University Hospital. She was scared she was losing control and needed help.

Ms. PRINCE: I didn't have health insurance. I had heard that this hospital, because it was a city hospital, that it had to take you, it had to give you care.

(Footage of Shalmah and Moriarty approaching hospital; hospital)

MORIARTY: *(Voiceover)* But Shalmah didn't get care. She was admitted, not as a patient, but as a test subject for psychiatric research and put in a locked unit known as 2 West.

Did you know at that point, right away, that you were gonna be part of a research trial, an experiment?

Ms. PRINCE: I've never heard of a research trial experiment. I mean, to me, experiments were something the Nazis did.

(Footage of signed consent form)

MORIARTY: *(Voiceover)* Still, Shalmah willingly signed a consent form...

Ms. PRINCE: 'Could you sign this for the doctor?' 'Oh, sure. Sure, I'll sign it,' you know. I didn't really read it.

(Footage of document)

MORIARTY: *(Voiceover)* ...a form stating that she would take part in a study of her illness, manic depression.

Did anyone make an attempt to call your parents?

Ms. PRINCE: No.

MORIARTY: Any family members?

Ms. PRINCE: No. Any doctor? No. Did they call my treating psychiatrist? No. Did they give me any other options? No. Did they tell me any of the risk? No.

Mr. GASTON COGSDALL: We trusted the doctors.

Mrs. COGSDALL: Yeah. We would not have even tolerated it had we known that it was research, you know.

MORIARTY: What both Shalmah and her parents know now is that she wasn't being treated for manic depression. Shalmah wasn't being treated at all. She was in a study of psychosis. The hospital's own records show Shalmah wasn't psychotic when she came into the emergency room. But five days later, she was.

‘Appeared distracted, jumped from topic to topic.’

Ms. PRINCE: Mm-hmm.

(Footage of Shalmah and Moriarty looking at medical records; footage of document with close-up of text: washed out)

MORIARTY: *(Voiceover)* Medical records show that when Shalmah was taken off, or ‘washed out,’ of lithium, her regular medicine, she began to act bizarrely.

‘She reports that she has been angry lately, but does not tell staff why. Several times in the interview, she burst out laughing.’

(Photo of Shalmah as child; footage of document with close-up of text: apomorphine; footage of painting)

MORIARTY: *(Voiceover)* And Shalmah got worse. Researchers who wanted to compare her brain chemistry to that of schizophrenics had injected Shalmah with a drug called apomorphine. She says it made her delusional.

Ms. PRINCE: *(Voiceover)* It hits you at the deepest level, you know?

You feel like you're coming internally undone, you know, and falling apart inside.

(Footage of painting; photo of Shalmah)

MORIARTY: *(Voiceover)* Shalmah became so paranoid and out of control at that point, she was put in restraints for three days.

Ms. PRINCE: Scary. It was frightening. You know, it was frightening. The abnormalcy, the danger of it was so clear.

MORIARTY: Had she ever been like this before?

Mrs. COGSDALL: Never, never, never, never, never.

Mr. COGSDALL: Oh, no, no, no.

MORIARTY: Has she ever been like that since?

Mrs. COGSDALL: Never, never, never.

Mr. COGSDALL: No.

Mrs. COGSDALL: Never, never. It was a result of what was injected into her at the time she was there.

MORIARTY: Why would someone like Shalmah Prince be injected with this kind of drug?

Dr. EDIL SCHAMU: Again, she was being used as a guinea pig because she went there for treatment, and apomorphine is not treatment.

(Footage of Edil Schamu)

MORIARTY: *(Voiceover)* Dr. Edil Schamu is a bioethicist at the University of Maryland, a scientist who believes that all non-therapeutic research on humans should be banned.

Dr. SCHAMU: We, as a society, have elected not to cause needless pain and suffering to animals. So why should we cause needless pain and suffering to these patients when this medicine is not in their benefit?

Ms. PRINCE: We were worse than animals.

(Photo of Shalmah; footage of hospital exterior)

Ms. PRINCE: *(Voiceover)* We were the perfect cover. These people, they're mentally ill.

They're the crazies.

MORIARTY: The doctor who ran the research unit at University Hospital, Dr. Jack Herschowitz, no longer works there and refuses to respond to Shalmah's claims. But in court documents filed after she sued him, Dr. Herschowitz insists that Shalmah entered the study willingly, that the doctors did nothing improper in it, and that Shalmah was actually dropped and given treatment when she became so ill and out of control.

Dr. SCHAMU: What's most unfortunate that this happens as I'm speaking to you now. It happens all the time on tens of thousands of patients.

(Footage of hospital; Steven Sirkowski and Paul Keck; Sirkowski and Keck with Moriarty)

MORIARTY: *(Voiceover)* Dr. Schamu says that like Shalmah, mentally ill patients coming to emergency rooms for treatment are still regularly recruited for research. Doctors Steven Sirkowski and Paul Keck say there's nothing wrong with that.

Dr. STEVEN SIRKOWSKI: Typically, in our hospital, almost everyone comes to the emergency room.

(Footage of hospital; photo of Shalmah)

MORIARTY: *(Voiceover)* They are researchers at the University of Cincinnati who, like those who handled Shalmah Prince's case, say even mentally ill patients can give informed consent.

Dr. SIRKOWSKI: There are some patients who get so very ill, they can't. But that isn't most patients.

(Footage of Sirkowski and Keck with Moriarty; document with close-up of text: Patients were paid; document with close-up of text: currently psychotic)

MORIARTY: (*Voiceover*) Yet they recently were criticized by advocates for the mentally ill for paying psychotic patients to undergo research before they were given treatment.

It says specifically here that the patients you're looking for are currently psychotic as evidenced by the presence of delusions, hallucinations or thought disorder.

Dr. SIRKOWSKI: Right.

MORIARTY: And these are the people who are giving you informed consent?

Dr. SIRKOWSKI: Right. And that—that—just because someone has those symptoms does not mean they're not capable of making life decisions. Patients will say, 'I don't want anyone else to have to go through this,' or, 'If this is something that might help me in the future, then I will do it.' I mean, that's—we hear those kind of comments all the time.

Dr. STEVEN HYMAN: I think the issue really is to understand whether that patient in that circumstance really can understand and make a reasoned judgment.

(Footage of Steven Hyman; National Institute of Mental Health; medical equipment; sign: Do not disturb experiment in progress)

MORIARTY: (*Voiceover*) Dr. Steven Hyman, who heads the National Institute of Mental Health, the government office that funds most psychiatric research, admits that too many studies have put people at risk. And he's done something about it at the institute.

What I understand, there were 108 studies that were in-house studies.

Dr. HYMAN: That's correct. Yes.

MORIARTY: And of those, 29 were shut down entirely...

Dr. HYMAN: That's correct.

MORIARTY: ...and 50 were rewritten.

Dr. HYMAN: Right.

MORIARTY: I mean, that sounds like a large number of studies that have problems.

Dr. HYMAN: It—it is—it is. It is a large number. I'm clearly not pleased with that—with—with those findings. But I felt we really had to have the very best possible standards.

(Footage of documents; Shalmah painting; footage of document with close-up of text: Dismissed)

MORIARTY: (*Voiceover*) And there will be 1,700 more studies around the country under review. In Shalmah's case, she lost the suit she filed against the doctors, alleging she was tricked into being a test subject. The judge ruled she waited too long to sue.

Doctors who conduct these experiments often say, 'Look, it was just two weeks of your life...

Ms. PRINCE: Yeah.

MORIARTY: ...15 years ago.'

(Footage of painting; photo of Shalmah)

Ms. PRINCE: *(Voiceover)* It was my identity. It was how my parents viewed me from then on. It was how I viewed myself.

I'm not out of it yet, you know.

(Photo of Shalmah; footage painting)

Ms. PRINCE: *(Voiceover)* I never came out of it. I'm not out of it yet, you know.

(Footage of Santana family at cemetery)

Announcer: *(Voiceover)* Still ahead, this family didn't know there was a problem...

Ms. MARIA SANTANA: I'm sure it was a nurse.

(Footage of building)

Announcer: *(Voiceover)* ...until they got an anonymous phone call.

Ms. SANTANA: ...and say, 'What's going on with Joseph?'

(Footage of ambulances; interior of hospital)

Announcer: *(Voiceover)* By then, they say, it was too late.

Ms. SANTANA: They are responsible for my brother's death.

(Photo of Joseph Santana)

Announcer: *(Voiceover)* That's next.

(Announcements)

HERE TO HELP?

ERIN MORIARTY: From the time a drug is first tested in human trials to the time it gets to the pharmacy is about seven years on average. But a system that may seem deliberate in some respects can still be lacking in others. For example, the government knows exactly how many guinea pigs are being used in animal research: 272,797. But officials have no idea how many people are the subjects of clinical research. Over the years, at least some protections have been written into law for pregnant women, for children, and even for some prisoners so they aren't exploited in testing. But I met one family that could only wonder: How could their loved one have taken the ultimate risk without even knowing it?

Unidentified Woman #1 (Joseph's Sister): These are beautiful. Happy Valentine's day, Joseph.

Unidentified Woman #2 (Joseph's Sister): He always was sharp. Always looked so cool.

Woman #1: That was because he had so many girlfriends, so it's like...

Woman #2: He was very good looking.

Ms. MARIA SANTANA (Joseph's Sister): We have great memories of him. And our last memories are not wonderful memories.

(Footage of Maria Santana and sisters putting flowers on grave; photo of Joseph; Bronx Psychiatric Center)

MORIARTY: *(Voiceover)* Maria Santana last saw her 36-year-old brother Joseph alive when she went to visit him on October 11th at the Bronx Psychiatric Center.

Ms. SANTANA: As soon as he saw me, he just started crying. He was like, 'Mita, mita, help me, help me.'

(Footage of ambulance; photo of Joseph; Jacobi Medical Center; doors closing)

MORIARTY: *(Voiceover)* An hour later, Joseph was rushed to an emergency room in a coma. Two days later, he died.

Ms. SANTANA: They killed my brother. I'm not saying they intentionally tried to kill my brother, but, yes, they—they are responsible for my brother's death.

(Footage of Santana with sisters at grave; Joseph's grave stone)

MORIARTY: *(Voiceover)* The Santanas say it was only after his death that they learned that Joseph had been part of a clinical trial for a new drug.

Woman #1: My brother was used as a guinea pig.

(Footage of Joseph's sister wiping her eyes at grave)

MORIARTY: *(Voiceover)* A drug so new and experimental...

Woman #1: Rest in peace.

(Footage of Joseph's sister laying down flowers at stone)

MORIARTY: *(Voiceover)* ...it didn't even have a name, just a number.

Woman #1: We're hurt and we're very angry.

Woman #2: He was well.

MORIARTY: It's been six months since Joseph Santana died, and his sisters still don't know how or why. The family's biggest question: Did Joseph, institutionalized with schizophrenia for 12 years, know and understand that he was part of an experimental drug trial?

(Footage of Center; photo of Joseph)

MORIARTY: *(Voiceover)* Joseph had been a patient at the Bronx Psychiatric Center since he was 24.

Ms. SANTANA: He still didn't know really right from wrong. He couldn't—you know, you really had to guide him.

MORIARTY: How old was he in this picture?

Ms. SANTANA: He was young.

(Footage of photos of Joseph)

MORIARTY: *(Voiceover)* Schizophrenia took away almost everything from Joseph.

Woman #1: My brother got sick in the '80s. He stood in the '80s.

(Footage of photo of Joseph)

MORIARTY: *(Voiceover)* Including his sense of time.

Ms. SANTANA: All he wanted to do was to shop for Sergios or Jordache.
(Footage of sisters talking around the table; pill being dropped on plate)

MORIARTY: *(Voiceover)* His sisters who took him out most weekends say Joseph had been taking Clozapine, an antipsychotic drug that seemed to be working.

Did any of you suggest to the doctors that he be taken off that drug?

Ms. SANTANA: No.

MORIARTY: Why?

Ms. SANTANA: He was doing good on it. He was able to communicate with us.

(Footage of photos of Santana family; Santana talking with Moriarty and showing pictures)

MORIARTY: *(Voiceover)* But sometime in September, Joseph was suddenly taken off Clozapine. The family only found out, Maria says, when she got an anonymous call.

Ms. SANTANA: I'm sure it was a nurse. That I know was a nurse.

(Footage of Santana talking)

MORIARTY: *(Voiceover)* Maria called his doctor...

Ms. SANTANA: I say, 'What's going on with Joseph?'

(Photo of Joseph)

MORIARTY: *(Voiceover)* ...who was also a researcher. And he told her that Joseph had agreed to try new medication.

Ms. SANTANA: If you told my brother, 'Throw yourself off the roof,' he would jump. He would do that.

(Photo of Joseph)

MORIARTY: *(Voiceover)* But the doctor insisted that Joseph did understand and had signed a consent form. The problem is...

Ms. SANTANA: My brother wasn't able to read anymore. What did he read? What'd—what did he read to sign?

(Footage of hospital records stating 'cannot read or write'; paper stating 'borderline' and 'mental retardation')

MORIARTY: *(Voiceover)* Hospital records confirm that and also state Joseph was in the borderline range of mental retardation.

Dr. EDIL SCHAMU (Bioethicist): These kind of experiments, let's face it, Erin, doesn't happen to your kids, my kids. They happen to the politically powerless, to the poor, uneducated, and the elderly, and the vulnerable, and the sick.

(Footage of Edil Schamu talking on the phone; of wired fence; the Center)

MORIARTY: *(Voiceover)* And it happens, says bioethicist Dr. Edil Schamu, because hospitals like the Bronx Psychiatric Center receive large grants from drug companies to test medications.

What if this had turned out to be a drug that would work for him better?

Dr. SCHAMU: But it didn't. Do you want to risk it?

(Footage of Santana sisters at grave site; photo of Joseph; pills dropping on a plate)

MORIARTY: *(Voiceover)* But without drug studies, there won't be new treatments. And, in fact, Joseph himself wouldn't have been helped by the drug Clozapine if it hadn't been tested on someone else a decade ago.

Ms. SANTANA: Joseph, don't worry. You're out of that hospital.

(Footage of Joseph's grave stone; report of autopsy; 'therapeutic complication' on report; letter to 48 HOURS to Mr. Josh Gelman)

MORIARTY: *(Voiceover)* In Joseph's case, the medical examiner ruled that he died from a lack of oxygen to the brain, a consequence of a course of drug treatment. In this letter to 48 HOURS, the drug company states: 'All laws and regulations were followed concerning patient consent.'

Ms. SANTANA: He's trying to tell us that my brother consented. The reason my brother is in the hospital is because he couldn't think for himself.

Bye, Joseph, we love you. We miss you. See you next weekend, OK?

(Footage of train moving on track; man walking in the snow)

Announcer: *(Voiceover)* Still to come, this homeless man has been in more than 10 drug studies.

Unidentified Man: There's no other way you can go out and work and make that kind of money that fast.

(Footage of paper stating 'Risks'; man walking in the snow)

Announcer: *(Voiceover)* So what could be wrong with that? We'll tell you next.

(Announcements)

GIVE ME SHELTER

(Footage of empty street in Baltimore; street light and sign, 'No Turn On Red' hanging in street; open window with curtains blowing outside; empty and rundown building; street sign, 'N. Milton'; police car driving on street)

TROY ROBERTS: *(Voiceover)* North Milton Avenue, one of the toughest streets on Baltimore's notorious east side.

Mr. ALAIN LAREAU (Drug Research Participant): The people that can move out of Baltimore have. And what's left of the people who can't move out, they have nowhere to go.

ROBERTS: *(Voiceover)* It's not the easiest place to live.

Mr. LAREAU: It's tore up, it's depressed.

ROBERTS: So this is it, huh?

Mr. LAREAU: Yeah.

(Footage of Troy Roberts and Alain Lareau talking outside of apartment; door with number '1114')

ROBERTS: *(Voiceover)* But Alain Lareau is just happy he's got a place to live. Anyplace.

Does it feel like home?

Mr. LAREAU: Yeah, it does. When I turn the key and go in, it's my place.

(Footage of looking out a window in bedroom; Lareau playing violin; empty street)

ROBERTS: *(Voiceover)* In fact, it's the first home Alain's had in two years since he hurt his back and lost his job as a mechanic. Within months, he had lost his apartment as well.

Where would you sleep?

Mr. LAREAU: Right in the corner.

(Footage of cemetery)

ROBERTS: *(Voiceover)* Alain was homeless.

Mr. LAREAU: It was very peaceful.

(Footage of Roberts and Lareau walking in the cemetery)

ROBERTS: *(Voiceover)* Living, of all places, in the local cemetery.

Mr. LAREAU: I thought I was just around the corner from being back on my feet. I didn't think it would have been this hard.

(Footage of Roberts and Lareau walking in cemetery; ad from Pharmakinetics)

ROBERTS: *(Voiceover)* But it was. Until he saw an ad in the paper for a new profession, human guinea pig.

What did the ad say, the first ad that you answered?

Mr. LAREAU: Pharmakinetics, take a vacation and earn money at the same time.

(Footage of Pharmakinetics office with 'Medical Screening' sign in window; Lareau smoking a cigarette)

ROBERTS: *(Voiceover)* Pharmakinetics, a private drug lab, hired Alain for two studies. He took experimental drugs for arthritis and high blood pressure. Altogether, he was paid \$2,200.

So these studies have paid for your rent here?

Mr. LAREAU: Yes.

ROBERTS: The food th—that you're eating now.

Mr. LAREAU: New shoes, glasses. Participation in this—in those studies got me this far.

(Footage of Lareau's bedroom)

ROBERTS: *(Voiceover)* But now Alain's broke again, and his rent is due.

How much money do you have on you right now?

Mr. LAREAU: About \$2.75.

(Footage of Lareau locking up apartment door; shadow of Lareau walking on the street; University of Maryland Medical Center; Lareau going into Medical Center)

ROBERTS: *(Voiceover)* So for \$1,400, Alain's agreed to be a human guinea pig again at the University of Maryland. He's testing an experimental vaccine for the dangerous cholera disease by actually ingesting cholera bacteria.

Mr. LAREAU: Well, this is it.

ROBERTS: You won't bow out at the last minute?

Mr. LAREAU: No. I would lose the money and lose my apartment.

ROBERTS: So you don't have a choice in this matter.

Mr. LAREAU: My choice is made.

Mr. ARTHUR CAPLAN (Bioethicist): What's the goal?

(Footage of Arthur Caplan teaching a class)

ROBERTS: *(Voiceover)* But Arthur Caplan, a bioethicist at the University of Pennsylvania, says a choice like that isn't a choice at all.

Mr. CAPLAN: We do exploit and take advantage of some of the most vulnerable members of society because it's the kind of work that the rest of us don't want to do.

(Footage of man carrying bags of bottles and cans; person pushing grocery cart full of cans; people living on the street)

ROBERTS: *(Voiceover)* He says all across the country, researchers are taking advantage of people like Alain, the desperate and the homeless.

Why are test subjects from the homeless population so attractive to these research companies?

Mr. CAPLAN: A homeless person who's got to struggle every day to make it through life without getting ripped off, beat up, run over, whatever happens to them, you tell them, 'Well, you know, there's some risk here that you might wind up with a bunch of scars on you or you might wind up with some liver damage down the road,' they're going to say, 'Hey, sounds a lot better than the lifestyle I'm living now. I guess I'll take that risk.'

(Footage of man leaning on snowbank)

ROBERTS: *(Voiceover)* Caplan's talking about guys like this.

Unidentified Man: You try their drugs and you don't know if it's good or not because you're doing it and it's not on the market yet. You're the guinea pig.

(Footage of train moving on the tracks; man walking on the street; Eli Lilly building; 'Informed Consent Document' paper; 'Risks' in bold print on form)

ROBERTS: *(Voiceover)* A homeless drug addict we met on the streets of Indianapolis. He asked us not to use his name or show his face. He says he's done more than 10 studies, most of them for the drug company Eli Lilly.

But, he says, he never even bothers to read the informed consent forms that lay out the health risks he's taking.

Man: They try to explain it to you. But you ignore everything they're saying because you're more worried about the money and getting into the study because you got other people competing with you. So you really don't care about what it is.

Mr. ED WEST (Eli Lilly Spokesman): Anything is possible. That is hard to believe.

(Footage of Roberts and Ed West walking in hallway and talking; elevator door opening up to Lilly Clinic)

ROBERTS: *(Voiceover)* Ed West is the spokesman for Eli Lilly. He says most of the company's test subject have homes, but the homeless are welcome, too.

Mr. WEST: We have chosen not to discriminate against people because they may be between residential addresses or they may be a homeless individual. The important thing is: Are they safe? Are they treated well? And can we debate the ethics of using a small number of those individuals in these trials? You bet we can debate it and we probably should.

(Footage of 'Eli Lilly and Company; Lilly Corporate Center' sign; man walking down sidewalk; 'Isolation Ward' sign on door)

ROBERTS: *(Voiceover)* But the debate gets even bigger, and it affects all of us. Ultimately, we're the ones who will take the medicines that have been tested on these human guinea pigs. But are those tests reliable?

Mr. DAVID PRYOR (Former Drug Research Participant): This used to be my home.

(Footage of David Pryor showing Roberts his old home under a bridge; Pryor playing saxophone)

ROBERTS: *(Voiceover)* David Pryor isn't so sure.

Mr. PRYOR: This is where I used to sleep.

ROBERTS: *(Voiceover)* These days, he plays in a California rock 'n' roll band, but for 15 years, he was a homeless alcoholic.

Mr. PRYOR: For the lack of any better word to call myself, a drunken wino.

(Footage of Pryor sitting where he used to sleep)

ROBERTS: *(Voiceover)* Pryor says he took part in five different drug studies, even though he was anything but an ideal test subject.

Mr. PRYOR: I'm scared to death one of these days, they're going to put a drug out here on these streets that's going to kill a lot of people because they had four winos up there that said, 'No, I don't have headaches. No, I'm not dizzy,' and they were.

(Footage of Lilly building; 'Exam' sign on door)

ROBERTS: *(Voiceover)* But Eli Lilly says it weeds out unhealthy test subjects.

Mr. WEST: If they meet the screens and the lab tests, then they can be enrolled. If they can't, then they can't.

Mr. LAREAU: Everybody was counting the hours.

(Footage of 'Center for Vaccine Development' sign in medical center; Lareau coming out of center carrying his violin case; Lareau coming outside of the James Lawrence Kernan Hospital)

ROBERTS: *(Voiceover)* Which brings us back to Baltimore and Alain Lareau. He went into the cholera study 11 days ago. Today, he's heading home.

How sick were you?

Mr. LAREAU: Not—actually, not so sick. M—mild flu.

(Footage of woman counting money; mirror showing Lareau at counter; woman counting money; Lareau and Roberts walking on sidewalk; cemetery)

ROBERTS: *(Voiceover)* In fact, he says, he'd do it again. And he might have to. The money Alain made in the cholera trial will keep a roof over his head for now, but it won't last forever.

Have you ever thought about the possibility of sleeping here again one day?

Mr. LAREAU: It's not an option. It won't happen.

(Footage of Lareau playing violin)

ROBERTS: *(Voiceover)* So he's already got his eye on another drug trial, testing malaria. That's right, malaria.

(Footage of older couple sitting in room; family around a wheelchair; woman; Santana sisters putting flowers on Joseph's grave and a photo of Joseph)

Announcer: *(Voiceover)* Still ahead, their lives were changed by a system they say has failed them. Are other families at risk?

(Footage of missile going into the sky; radar photo of target; American POWs; Dan Rather reporting; bomb explosion)

Announcer: *(Voiceover)* Also ahead, it's an undeclared war: Dan Rather at ground zero.

(Announcements)

(Footage of man in wheelchair; older man with woman in chair; woman staring; Joseph Santana' grave; photo of Santana)

ERIN MORIARTY: *(Voiceover)* The people you've met tonight say they and their families are victims of a system that failed to protect them, a system that by many accounts is breaking down.

Last month, in a milestone for those seeking reform, the Veteran's Administration suspended hundreds of experiments at a Los Angeles VA hospital to protect patients. No one questions the need to conduct human testing for drugs and devices that are intended to treat humans, but until there are effective reforms, it will depend largely on the good faith of doctors and scientists to make sure that those who participate in vital human testing are treated like human beings.

Before we leave you tonight, we'd like to share a personal report from Dan Rather in Belgrade, Yugoslavia. Ground zero in the war over Kosovo. **DAN RATHER**: Once upon a time, it was said those who won the war got to write the history. The losers merely wrote the legends. But that was in the days before instant communications. Nowadays, history writes itself inside the television camera. Afterwards, the combatants compete to interpret the truth and juggle the facts.

(Footage of NATO-destroyed convoy in Kosovo; refugees crying; boy crying; body in field; belongings of refugees; men carrying mattress with bodies; boy crying; plane flying overhead; men picking up body; men carrying injured refugee; men putting body on cart; injured refugees in cart; NATO-bombed train; radar film of train being bombed from plane; bombed train; injured in hospital; refugees in camp; refugees lined up at border standing under makeshift tent; military passing out food to refugees; refugees in tent; children sitting with each other; tired female refugee)

RATHER: *(Voiceover)* NATO and the Serbs have spent the past 24 hours juggling the available facts surrounding attacks on two refugee convoys in western Kosovo. Serbs blame NATO for both attacks. NATO accepted blame for one of them. The villages of Djakovica and Zrce have entered the history books. But in the process, the colossal misery involved has begun to be sidelined. This railway bridge, too, has entered the history books. As we watch the crosshairs mix and match and cause the bridge and a loaded train to vanish forever, we are mesmerized by the technology. History has again been written in fact and detail. But apart from expressions of regret, we know nothing of the souls traveling on the train. In this war over Kosovo, we know where many of the refugees are and why. We even know what they will eat and where some of them will sleep tonight. But we still do not know enough. This may be a war over humanitarian principles, but its history will be of facts rather than humanity. It will be about what we know, not what we understand.

Now, there's a downside to all this. Communications technology may be helping to write the history, but what tends to get lost in all the confusion of facts, exaggeration, claims, counterclaims and half-truths, is one of the basic tenants of civilization; that is understanding.

Before you can hope to end a war, you must first understand those who are fighting it. We know from history that knowing everything, but understanding nothing, is recipe for disaster.

That's 48 HOURS for tonight. I'm Dan Rather. Thanks for choosing CBS. I'll see you again tomorrow on the "CBS Evening News." From Belgrade, Yugoslavia, good night.

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Testimony of
J. Thomas Puglisi, Ph.D.
Director
Division of Human Subject Protections,
Office for Protection from Research Risks,
Office of Extramural Research,
National Institutes of Health,
U.S. Department of Health and Human Services

Before the
Subcommittee on Oversight and Investigations
and Subcommittee on Health,
Committee on Veterans' Affairs,
U.S. House of Representatives

Wednesday, April 21, 1999
334 Cannon House Office Building
10:00 a.m.

FOR RELEASE UPON DELIVERY

Mr. Chairman and Members of the Subcommittees:

I am Tom Puglisi, Director of the Division of Human Subject Protections, Office for Protection from Research Risks (OPRR), Office of Extramural Research, National Institutes of Health (NIH). I am accompanied by Gary B. Ellis, OPRR's Director. We are pleased to appear before the Subcommittees to report on OPRR's oversight of protection of the rights and welfare of human research subjects at the Veterans Affairs (VA) Greater Los Angeles Healthcare-System.

In 1995, I headed a site visit to the VA West Los Angeles, which led to the events giving us cause to meet this morning. Dr. Ellis chairs the Interagency Committee on Protecting Human Research Subjects (known formally as the Subcommittee on Human Subjects Research, Committee on Science, National Science and Technology Council), of which the VA is an active member.

This Spring marks the 25th anniversary of the promulgation in 1974 of the Department of Health and Human Services (DHHS) regulations for Protection of Human Subjects in research (Title 45, Code of Federal Regulations, Part 46; May 30, 1974) and the enactment of the National Research Act (Public Law 93-348; July 12, 1974). At their core (Subpart A), the DHHS regulations contain requirements for assuring compliance by research institutions; requirements for researchers obtaining and documenting informed consent; and requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping. The DHHS regulations also contain additional protections for certain vulnerable research subjects--pregnant women (Subpart B), prisoners (Subpart C), and children (Subpart D).

The "Common Rule"

In 1991, the core DHHS regulations (45 CFR Part 46, Subpart A) were formally adopted by more than a dozen other Departments and Agencies that conduct or fund research involving human subjects as the Federal Policy for the Protection of Human Subjects, or "Common Rule." In 1991, the Department of Veterans Affairs promulgated this rule at 38 CFR Part 16. Today, the 1991 Federal Policy is shared by 17 Departments and Agencies¹, representing most, but not all, of the federal Departments and Agencies sponsoring human-subjects research.

¹Agency for International Development; Central Intelligence Agency; Consumer Product Safety Commission; Department of Agriculture; Department of Commerce; Department of Defense; Department of Education; Department of Energy; Department of Health and Human Services; Department of Housing and Urban Development; Department of Justice; Social Security Administration; Department of Transportation; Department of Veterans Affairs; Environmental Protection Agency; National Aeronautics and Space Administration; and National Science Foundation.

In addition, certain federally sponsored and much privately sponsored research is subject to the regulations of the Food and Drug Administration (FDA) at 21 CFR Parts 50 and 56. FDA regulations confer protections on human subjects in research when a drug, device, biologic, food additive, color additive, electronic product, or other test article subject to FDA regulation is involved. FDA regulations and the provisions of the Common Rule are largely congruent, although some significant differences exist.

The Common Rule defines "research" as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." Activities which meet this definition constitute research for purposes of the Common Rule, whether or not they are conducted or supported under a program which is considered research for other purposes. Some demonstration and service programs, for example, may include research activities.

The Common Rule defines "human subject" as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information."

Institutional Review Boards

The cornerstone of our system of protection of human research subjects is the local Institutional Review Board at the research site. The IRB is, by federal regulation, to consist of a minimum of five people, including at least one scientist, one nonscientist, and one person not otherwise affiliated with that institution. The nonscientist must be present to achieve a quorum. The members must have varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.

The IRB must be sufficiently qualified through the experience, expertise, and diversity of its members to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB must be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB must therefore include persons knowledgeable in these areas.

Under the Common Rule, 17 federal Departments and Agencies cannot provide funds for human subjects research unless an IRB approves the protocols for such studies. No human-subjects research supported by a Common Rule Department or Agency may be initiated, and no ongoing research may continue, in the absence of an IRB approval.

Let me turn briefly to the specific responsibilities of the Institutional Review Board. IRB review assures that:

- risks to subjects are minimized;

- risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result;
- selection of subjects is equitable;
- there is proper informed consent and documentation of informed consent;
- when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects;
- when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and
- additional safeguards have been included in the study to protect the rights and welfare of any subjects likely to be vulnerable to coercion or undue influence

Once research is initiated, IRBs have continuing responsibilities. These include:

- The conduct of continuing review at intervals appropriate to the degree of risk, and in any event, not less than once per year.
- Authority to observe or have a third party observe the consent process and the research.
- Receipt of prompt reports from investigators of any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with the IRB's requirements or determination, or with the regulations.
- Authority to suspend or terminate IRB approval of research that is not being conducted in accord with the IRB's requirements or that has been associated with unexpected serious harm to subjects.

Informed Consent

All present today know how integral--how crucial--the process of informed consent is. Many have a general picture of informed consent, and it is useful to add higher resolution to that picture. Federal regulations specify 14 elements of informed consent, 8 of which are required:

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- (2) A description of any reasonably foreseeable risks or discomforts to the subject.
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
- (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- (8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

A researcher who seeks to recruit an individual for research without conveying all of these elements of information in language understandable to the potential subject is not obtaining *informed consent*.

Assurance of Compliance

Within DHHS, OPRR oversees implementation of the human-subject regulations in all DHHS facilities as well as domestic and foreign institutions or sites receiving DHHS funds. In keeping with the provisions of the Common Rule, OPRR requires that each DHHS agency and extramural research institution that conducts research involving human subjects sets forth the procedures it will use to protect human subjects in a policy statement called an "Assurance" of compliance. Under the Common Rule, OPRR has authority for approving an Assurance at DHHS-funded institutions for federal-wide use.

An Assurance with OPRR is a formal, written commitment to: (1) widely held ethical principles; (2) the DHHS Regulations for Protection of Human Subjects; and (3) institutional procedures adequate to safeguard the rights and welfare of human subjects. The terms of the institution's Assurance are negotiated with OPRR.² The detailed, written Assurance statement becomes the instrument that OPRR uses to gauge an institution's compliance with human subject protections

²OPRR utilizes several types of Assurance documents. Multiple Project Assurances cover all of an institution's federally-supported research. Cooperative Project Assurances cover participation in DHHS-supported multicenter clinical trials. Single Project Assurances cover individual DHHS-supported projects.

if there is a problem. Where noncompliance has occurred, OPRR has the authority to require corrective actions under the Assurance or to withdraw its approval of the Assurance.

At OPRR's discretion, institutions with a large volume of research and demonstrated expertise in human subjects protection may be granted a Multiple Project Assurance (MPA). A Multiple Project Assurance, as the term implies, is an institution's pledge of full human subject protections for multiple projects at the institution.

At present, OPRR holds some 430 Multiple Project Assurances that cover some 730 research institutions in the United States and Canada. Most of these Multiple Project Assurances, at the voluntary election of the research institution, commit all activities at the institution--irrespective of funding source--to the DHHS regulations for Protection of Human Subjects. OPRR appreciates the willingness of many institutions to choose this voluntary option.

From 1987 to 1998, the VA West Los Angeles held Multiple Project Assurance #M-1097, and the VA Sepulveda held Multiple Project Assurance #M-1292. [First approved in 1982, MPA #M-1097 initially covered only the Wadsworth facility. The Sepulveda MPA #M-1292 was first approved in 1983.] Coincident with an administrative merger and at the request of these institutions, a new Multiple Project Assurance, #M-1087, was approved in 1998 for the VA Greater Los Angeles Healthcare System.

On March 22, 1999, OPRR deactivated Multiple Project Assurance #M1087 for reasons I will describe in a moment. First, I will describe the history of OPRR's interaction with the VA West Los Angeles.

OPRR's oversight of compliance by the VA West Los Angeles with DHHS human-subject rules

In 1993, as OPRR was investigating informed consent in schizophrenia research at the University of California Los Angeles, OPRR received an allegation that informed consent procedures for schizophrenia research at the VA West Los Angeles also failed to meet regulatory standards. Upon investigation, OPRR found that numerous informed consent documents lacked basic, required information such as a complete description of (i) the procedures for manipulation and withdrawal of medications; (ii) reasonably foreseeable research risks; and (iii) potentially advantageous alternatives to research participation.

OPRR required correction of these deficiencies in July 1994. OPRR also required that the VA West Los Angeles implement four additional protections for subjects of psychiatric research; specifically, (i) that the IRB include, at every meeting where such research is reviewed, a special representative who could give voice to the perspective of potential subjects in safeguarding their rights and welfare; (ii) that informed consent documents disclose when medication is determined by the research protocol rather than by clinical need; (iii) that informed consent documents disclose when the treating clinicians are also the research investigators; and (iv) that a special Data and Safety Monitoring Board (DSMB) be established to monitor such research (i.e., where the treating clinicians are also the research investigators). The VA West Los Angeles agreed to

implement these corrective actions, and its Multiple Project Assurance was restricted to require quarterly progress reports to OPRR documenting implementation.

In January 1995, I led an OPRR site visit to the VA West Los Angeles. The site visit revealed a number of deficiencies in the Institutional Review Board's operating procedures and record-keeping practices that undermined the effectiveness of systemic protections for human subjects. These deficiencies included (i) inadequate monitoring of changes required by the IRB; (ii) inappropriate designation of exemptions; (iii) inappropriate use of expedited review procedures; (iv) inadequate continuing review procedures; and (v) inadequate procedures for reporting unanticipated problems involving risks to subjects or others. The site visit also revealed the need for (i) a comprehensive education program for IRB members and investigators; and (ii) increased support staff for the IRBs.

These findings were communicated to VA West Los Angeles officials orally at the conclusion of the site visit, and in writing on February 14, 1995. The facility's Multiple Project Assurance remained restricted, and quarterly progress reports documenting appropriate corrective actions were required.

OPRR continued to receive progress reports from the VA West Los Angeles in 1996, but no progress reports were received in 1997. OPRR requested additional information in April 1998, because it was still not clear that all required actions had been successfully implemented. The VA West Los Angeles provided reports to OPRR in June and November 1998.

Review of this information by OPRR revealed continuing, serious deficiencies in human subject protection procedures at the West Los Angeles facility. In specific, OPRR reviewed the minutes of 9 IRB meetings conducted in May, June, and July 1998. OPRR found that in 7 of those 9 meetings, the IRB conducted business (i.e., approved human subjects research) without a valid quorum, either because a majority of members failed to appear or because there was no nonscientist member present, as the regulations require. Two of those meetings lacked both a numerical quorum and a nonscientist member.

In addition, you will recall that in 1994 OPRR required that the IRB include a special subject representative when reviewing psychiatric research. In OPRR's 1998 review of 9 IRB meetings, 1 of the 3 meetings at which psychiatric research was approved failed to include such a representative.

Moreover, OPRR found that the VA West Los Angeles failed to document implementation of the 1994 requirement for a Data and Safety Monitoring Board to oversee psychiatric research. In fact, the VA West Los Angeles Policy and Procedure Manual for Human Subjects Research, provided to OPRR in November 1998, states that "DSMB monitoring procedures have not been finalized yet" (page 22), 4 years after OPRR imposed the requirement.

In addition, OPRR was concerned that individual IRB members did not appear to be receiving and reviewing sufficient written information to ensure substantive continuing review of research, as the DHHS human subjects regulations require. In specific, the VA West Los Angeles Policy

and Procedure Manual for Human Subjects Research states that such information need only be reviewed by one member (page 23). OPRR further found that the IRB minutes failed to document any discussion of research protocols during continuing review.

OPRR also determined that expedited review procedures, which are permitted only for certain specified categories of minimal risk research, were still being used inappropriately, 4 years after OPRR had brought this issue to the attention of the VA West Los Angeles IRBs.

OPRR's action of March 22, 1999

In view of the extended history of concerns and as a result of these latest findings, OPRR concluded that more stringent oversight was needed of DHHS-supported human subjects research involving the VA Greater Los Angeles Healthcare System. Therefore, OPRR deactivated the VA Greater Los Angeles Healthcare System Multiple Project Assurance (#M-1087). This action, effective March 22, 1999, removed the Assurance required for conduct of federally supported human subjects research.

OPRR directed the VA Greater Los Angeles Healthcare System to suspend enrollment of new subjects in all DHHS-supported research, except in extraordinary cases verified by OPRR to be in the best interests of an individual subject. Research activities involving previously enrolled subjects were allowed to continue where continuation is in the best interests of individual subjects.

DHHS-supported human subjects research may resume at the VA Greater Los Angeles Healthcare System only under new Assurance mechanisms that entail either (i) OPRR review of individual protocols and informed consent documents (i.e., the Single Project Assurance mechanism); or (ii) oversight by a collaborating institution's IRB under the approval of OPRR (i.e., the Interinstitutional Assurance mechanism).

Enrollment of subjects in DHHS-supported research may not resume until acceptable Assurance mechanisms have been approved by OPRR. However, OPRR stands ready to proceed under such mechanisms as soon as the VA Greater Los Angeles Healthcare System certifies valid IRB review and approval of each of its DHHS-supported human subjects projects. OPRR notes that on April 6, the VA requested, and OPRR granted, a 3-month extension of OPRR's deadline for VA conduct of these reviews.

OPRR oversight of other human-subject protections at other VA facilities

As I indicated previously, OPRR has authority under the Common Rule for approving an Assurance at DHHS-funded institutions for federal-wide use. When an Assurance approved for federal-wide use is on file with OPRR, other Department and Agency heads, including the Department of Veterans Affairs, rely on that Assurance of an institution's compliance with the Common Rule.

At present, 41 VA facilities hold Multiple Project Assurances that are approved by OPRR for federal-wide use. Some 50 VA facilities are covered under other Assurance mechanisms that are limited to specific categories of DHHS-supported research.

OPRR is currently conducting 3 compliance oversight investigations that involve VA facilities; specifically, (i) the James A. Haley VA Hospital, in association with the University of South Florida in Tampa; (ii) the Philadelphia VA Medical Center; and (iii) the Cincinnati VA Medical Center, in association with the University of Cincinnati. The Tampa research involves nephrology experiments on salt regulation; the Philadelphia research involves cardiology research; and the Cincinnati research involves psychiatric research.

I am not able to comment further on these ongoing investigations because OPRR has not yet reached any determinations of fact in these cases. OPRR will be happy to inform the Subcommittees as soon as such determinations have been made.

OPRR recently completed a complex investigation of several DHHS-supported psychiatric research projects at the VA Medical Center in the Bronx, New York. DHHS-supported research at the Bronx VA is covered under the Mount Sinai School of Medicine Multiple Project Assurance. OPRR determined that the informed consent documents for these projects failed to provide adequate descriptions of the research purpose; the research procedures; the reasonably foreseeable risks and discomforts of the research; and the potentially advantageous alternatives to research participation. Subjects in one of these projects, conducted in the mid-1980s, suffered at least some short-term harm or discomfort in the form of an exacerbation of psychiatric symptoms.

OPRR determined that appropriate corrective actions have been implemented by Mount Sinai Medical Center and the Bronx VA to ensure compliance with DHHS regulations in current and future research. Among these actions are the adoption of specific guidelines for research involving medication withdrawal or washout, including requirements that (i) an independent health professional must assess each prospective subject's capacity to consent prior to enrollment; (ii) an independent physician must monitor each subject's participation in the research; and (iii) the risks of drug withdrawal, placebo administration, and experimental drugs must be included.

Conclusion

Our enduring and vigorous system of protection of human research subjects is designed to prevent physical injury, psychological injury, and harm to the dignity of research subjects, as biomedical and behavioral scientists pursue new knowledge for the common good. We are always interested in improving the system to make research as safe as it can possibly be.

Of special interest today are the rights and welfare of human subjects under the auspices of the Department of Veterans Affairs. OPRR does not have either an immediate or an historical basis for distinguishing compliance of those VA medical centers under its purview, as a class, from other biomedical and behavioral research institutions.

It is abundantly clear, however, that VA medical centers have a profound obligation to ensure that our nation's veterans are afforded the highest possible levels of protection when they become subjects of research. To the extent that any research conducted at VA facilities involves any veteran-subject who may be vulnerable to coercion or undue influence for any reason, the VA has a special responsibility to provide particularly stringent protections. In formal, Common Rule language, such vulnerability requires that "additional safeguards have been included in the study to protect the rights and welfare of these subjects." Clearly, the VA must set its aim well beyond minimal compliance with regulatory standards.

In the final analysis, Mr. Chairman and Members of the Subcommittees, research investigators, institutions, and we are stewards of a trust agreement with the people who volunteer to be research subjects. We have a system in place that strives, to the greatest degree possible, to (i) minimize the potential for harm; (ii) enable and protect individual, autonomous choice; and (iii) promote the pursuit of new knowledge. By doing so, we protect the rights and welfare of our many citizens who make a remarkable contribution to the common good by electing to volunteer for research studies. We owe them our best effort.

Thank you, Mr. Chairman. We are pleased to answer any questions about our system for safeguarding the rights and welfare of human research subjects.

For additional information about protection of human research subjects, see:
www.nih.gov/grants/oprr/oprr.htm

**The House Committee on Veteran's Affairs
Oversight and Investigations Subcommittee**

Ladies and Gentlemen:

My name is Dr. Stephen Pandol. Thank you for hearing my statement today. There have been innumerable erroneous allegations made towards the Research Administration of the VA Greater Los Angeles Healthcare System. My purpose today is to provide important factual information and to submit to you suggestions that may be useful in improving the performance and safety of biomedical research for the Department of Veterans Affairs. The information I will present is from our own experience at the West Los Angeles VA Medical Center but it will have implications for the system at large.

For approximately three years I held the position of Director, Research and Development at the West Los Angeles VA Medical Center. As of late last year this Medical Center was incorporated in to the VA Greater Los Angeles Health Care System and I was appointed Acting Associate Chief of Staff for Research and Development for the System. I was reassigned to the position of staff physician on March 23, 1999, with official notification on March 30th. In addition to my administrative post, I am a clinician, medical researcher and educator. I have performed fundamental research on pancreatic disorders for approximately 20 years and currently hold grants with both VA and NIH.

When I started the position in Los Angeles, I had a vision of developing a research department that worked in collaboration with the medical care mission of the Medical Center. The result would be an acceleration of improvements in health care for our veterans as well as our nation. I believed this approach was completely consistent with the goals for the VA nationally. This approach was supported and encouraged by the Director of the facility, Ken Clark. Furthermore, I felt that we had both the size and the potential talent pool to accomplish this task.

Upon taking the position, I was assured that severe administrative problems that had plagued the Research Department for years had been resolved. From the beginning, however, I was aware that a major issue that had to be dealt with was the replacement of the research buildings – a goal that the Medical Center had not been able to accomplish since at least 1984. Even at that time, the structures were felt to be unsafe and out-of-date. We submitted a building replacement request in 1988 to which no response has been received to date.

Over the next few months I discovered several problems in the research program that were serious and were having a significant negative impact on its performance. These were all reported to management. They included:

1. A lack of oversight of human research resulting in a serious risk liability
2. A financial system in the Research Department that had collapsed. In addition, there was a large accumulated debt.
3. A very low rate of successful funding of VA grants for our investigators.

Our Research Administration has made substantial progress in resolving each of these problems. I will discuss each below and show that they had interconnecting effects on each other.

Oversight of Human Subject Research

Within days of arriving, I heard about problems in cardiology and cardiology research. I also found out that there had been an investigation of the problems, but I was informed by some individuals that the investigation was a "whitewash." Despite resistance within the Organization, I halted the research of three cardiology investigators and demanded of the Chief of Staff that there be a more extensive investigation. The Chief of Staff agreed and established a Board of Investigation to review allegations and improprieties. The Board of Investigation lasted approximately six months and included representation from the VA Headquarters Office (Dr. Pam

Steele). The Chief of Staff requested that I not be a member of the Board of Investigation. However, the Chief of Staff asked me to implement certain actions that were recommended by the Board. These actions included specific supervision of Dr. Phillip Sager and developing a program of quality assurance and oversight for human research. Both were instituted.

I would note that I notified Dr. Generty, Special Assistant to Chief Research and Development Officer, about the Cardiology case in October of 1998, when we were contacted by the LA Times about the case. Dr. Generty indicated that there was nothing additionally he felt that we should do.

From the results of the Cardiology Board of Investigation and other observations, I was aware that oversight was lax and that the Organization faced significant risk because of this lack of oversight. Examples of general problems included a lack of pharmacy supervision of research pharmaceuticals and lack of compliance of research sites to regulatory standards. Professional staff was hired for oversight. One person was a clinical Ph.D. in psychology with training and experience in good clinical practice techniques in human research. This person became the Manager of Scientific Affairs. The other was a clinical pharmacist who reported to the Manager. In addition, we formed a Clinical Research Center (CRC) Committee with the purpose of ensuring that all environments where human research was practiced met regulatory standards and were safe. The CRC had an assigned Director and the Committee had a Chairman. All investigators performing human research were encouraged to participate. The research staff, the CRC Director and committee all participated to ensure that all research was performed in "approved" sites and that practices by investigators met regulatory standards. Training of investigators and clinical coordinators was also instituted and included standards on the performance of informed consent, confidentiality of patient records, subject privacy, proper documentation of inclusion and exclusion criteria, the use of experimental pharmaceuticals, and safety in the clinical care environment. To accomplish these goals there have been both one-on-one instructions of investigators and clinical coordinators as well as group training sessions. Recent spot audits demonstrate excellent compliance with standards.

In addition to actions taken to improve the safety of human research, all IRB Board members received copies of VA, OPRR, and FDA regulations pertaining to human subject research and many also viewed videos explaining OPRR standards and practices. Some IRB members have attended OPRR-sponsored training seminars to further enhance our understanding and practice of oversight.

I took another step to show my commitment to quality of care and safety in the Organization. With the encouragement of the Medical Center Director, Ken Clark, I provided a leadership role in the Quality Assurance program for the entire Medical Center. In this role, I provided an example for those involved in research to participate in improving the quality of patient care in the hospital. Our participation helped the hospital win the VA's Carey Award for Quality and Performance Improvement in 1997; and receive Accreditation with Commendation from the Joint Commission of Accreditation of Hospitals in 1998.

The measures described above have had a significant impact on improving the safety and performance of human research in the Organization. I firmly believe that our activities serve as a model for ensuring quality and safety of human research nationally. I should note that these improvements were accomplished despite obstacles in the Organization to obtain resources to perform oversight functions. This issue is discussed in more detail in the next section on financial issues.

The action by OPRR to rescind our Multiple Project Assurance status was based on misinterpreted and out-of-date information. For example, the report indicated the lack of a subject representative on the mental health human subject review board when in fact there has been a dedicated subject representative for well over four years. Another example, OPRR found that some review board meetings had taken place without a quorum present. Corrective action

was taken in August of 1998 to dramatically improve performances in this area. There are many other examples where OPRR failed to recognize improved procedures at the facility.

A major issue raised by OPRR was a lack of responsiveness by our Medical Center to addressing issues related to a "restriction" placed by OPRR on the Mental Health IRB. OPRR's investigation of the VA Mental Health IRB was a consequence of their investigation of UCLA's IRB following the suicide of a research subject participating in a UCLA-approved study. The Mental Health IRB and its "restriction" were part of the Brentwood VA Medical Center. This IRB became incorporated into the West LA Medical Center in 1996 when the Research Department of Brentwood and West Los Angeles VA Medical Centers were consolidated. Neither the Chief of Staff, who is my direct supervisor, predecessors in my position or the Headquarters Research and Development Office informed me of the "restriction". Furthermore, by its own admission in a letter dated April 20, 1998, OPRR admitted to not communicating with the Medical Center for a two year period and apologized for doing so. Essentially, OPRR had not responded to requested documentation from the Medical Center submitted to OPRR in 1995 and early 1996 until mid 1998. In late August 1998 the research staff became aware of the OPRR "restriction" through a letter to the Medical Center Director from OPRR. The letter stated that changes in IRB policies and procedures requested in 1995, had not yet been fully addressed. Because we had none of the previous OPRR documents, our office was forced to request that OPRR fax us a copy of the 1995 letter. In November of 1998 we submitted an extensive packet of material for OPRR's evaluation. In February of 1998 we contacted them asking if they needed further material on our progress or any clarification. We were told that the material had not yet been evaluated. No further communication occurred until the announcement that the Multiple Project Assurance Status was rescinded. More timely communication or a site visit would have provided an opportunity to more adequately address concerns.

Of note is the fact that VA Research and Development does not provide national training in human research standards and compliance. Furthermore, in September 1998, we notified Dr. Gerrity about the "restriction" and requested assistance in responding in terms of improving our institution's operating manual for human research. Dr. Gerrity indicated that Headquarters did not have the ability to provide such assistance.

Financial Issues

Within the first few months of my tenure, I discovered a history of gross financial mismanagement of the department. I found that the previous Research Management did not consistently provide financial statements to investigators for their research. Further, I was receiving daily phone calls from creditors for old bills, and I ultimately discovered that the Department had an approximate \$2.5 million debt. This amount was an extraordinary debt burden because most of the money that comes to the research appropriation was directed to the grants and contracts. Only about \$500,000 annually was provided for research administration. The most glaring issues leading to the debt we inherited were that there were several high salaried research staff on the rolls without resources from grants to pay for these salaries. The other factor that led to the debt burden was the fact that research administrative services were provided to other agencies and organizations without compensation. These included our own nonprofit research corporation, UCLA and National Institutes of Drug Abuse or NIDA. The VA research appropriation only provides research administrative support funds for grants funded by VA. Less than 25% of our research portfolio was VA funded. I estimated that about one half of our research administrative costs were related to non-VA funded projects.

In order to address all of these issues, we instituted the following measures:

- A. I notified the Chief of Staff, Dr. Norman, The Director of Business and Finance, Lynn Carrier, the Medical Center Director, Ken Clark and the Medical Center Financial Office of the problem.

- B. The first action was to conduct a reduction-in-force to decrease the salary burden. The request for this action took place within the first few weeks of my arrival.
- C. I hired a qualified Administrative Officer and Financial Manager to determine the nature of the financial and personnel problems.
- D. These individuals performed in-depth reviews of all grants, budgets and staffing levels to determine the financial condition of the research appropriation. Included was a review of over 5,000 obligations and reconciling several hundred accounts dating back to 1994. Several thousand-man hours of Research Department effort were devoted to targeting the problems and correcting them, despite extremely limited resources. The results were communicated to local, VISN and VA headquarters staff.
- E. After exhausting all efforts to resolve the inherited financial condition, the last resort toward stabilization (including paying inherited debt) required reduction of research administrative expenses and staff by 1/3. These actions prevented an end of year deficit. These reductions were implemented despite the large workload required to rectify the financial and personnel problems and the large increase in the number of grants obtained recently. The overall effect compromised our ability to perform administrative functions (including those involved in IRB and oversight) in an optimal manner. I notified the Chief of Staff about this problem on several occasions. Notification included suggestions to rectify the problems through revenue enhancement and retrieving compensation for administrative services provided to our nonprofit research corporation, UCLA and NIDA.

In addition to the above, a variety of other actions were initiated to rectify the personnel and financial problems. These included:

1. Stopping all unfunded research activity
2. Reducing staff by further reductions-in-force, terminations and buyouts.
3. Developing cost sharing arrangements with the Medical Center to optimize the use of staff and minimize the cost to research
4. Installing financial and budgetary controls.
5. Negotiating payment plans with all creditors.
6. Initiating MOU's and sharing agreements with the VA nonprofit research corporation, UCLA, NIDA and companies to recover costs incurred in both the research appropriation and medical care appropriation.
7. Providing financial statements to investigators on a quarterly basis.

Although we initiated MOU's and sharing agreements, implementing them was a struggle even though an IG audit done at the Medical Center before my arrival demanded mechanisms to appropriately reimburse the Medical Center for research-related costs. There was no action taken to resolve the issues raised by the IG prior to my arrival. Obstacles were present both internally (i.e. nonprofit research corporation) and with the outside organizations (i.e. UCLA and NIDA). The following are some examples. We estimated that the costs of support for IRB's and human research oversight for projects from our VA nonprofit research corporation were about \$200,000 per year. This amount was supported by an independent audit by the Medical Center's Chief Financial Officer. Despite his corroboration, the Executive Director of the nonprofit, the Chief of Staff and acting Deputy ACOS for Research argued that the support could be provided with significantly less staff and a third to one-fourth of the cost.

This argument took place over a two-year period during several nonprofit research corporation Board meetings. At one meeting in 1998, I stated that since there was disagreement on the amount of resources needed to provide IRB support and human research oversight, that we should invite OPRR to provide a consultation on staffing and functions. The Medical Center CEO ordered me and other members present not to contact OPRR.

An agreement for pay-in-kind for services provided to the nonprofit by the Research Department was reached in late 1998. This agreement had the potential to stabilize staffing in the Research Department related to IRB and humans research oversight functions. However, at its January 1999 meeting, the Chief of Staff indicated that the nonprofit research corporation was not obligated to provide the support. Legal counsel, in addition, indicated that there was no legal mechanism to provide payment to research.

I argued the case for stable support so vigorously that I was admitted to the hospital the next day with my first episode of unstable angina requiring coronary vascular repair.

Of note: we notified both Drs. Burris and Gentry at Headquarters Research and Development during 1998 of our difficulty in assuring stable funding to support IRB and human research oversight.

The agreement with the nonprofit was critical because we estimated that 60% of our work load related to human research was due to nonprofit research corporation contracts and grants.

We have continued pursuing the development of a sharing-agreement with UCLA. About one year ago, I reached an agreement with UCLA to proceed with establishing a mechanism for such payment using the Enhanced Sharing Authority. The research staff developed a proposed contract that is presently being evaluated for negotiation in our business office. This contract contains recovery of costs of between \$3 - 4 million to both the Medical Care and Research Appropriations. Even at this time research administrative services are being provided to support UCLA grants and contracts at the VA Medical Center without compensation. The effect is a diminished research administrative staff trying to support all of the research performed at the VA Medical Center.

Acquisition of payment for services by NIDA was difficult at best. NIDA argued that they had no requirement to pay for research administration services as well as refused to have the research department provide oversight of their human research. I insisted that there be appropriate oversight by the research department because of my concern about their vulnerable subject population - cocaine addicts. Continued disagreements about payment for research administrative services and issues related to noncompliance oversight led to the removal of this program from our site.

Despite the obstacles described above, research management accomplished a complete restoration of the financial system, resolution of the debt and established a stable administrative staff. As indicated above, the staff needs further resources to function optimally.

Investigator Grants

The Medical Center was considered one of the premier research sites in the VA system in the 1960's, 1970's and early 1980's. As indicated earlier there had been a dramatic decline in the performance of researchers, especially in obtaining VA funded grants prior to my arrival. This issue had to be corrected or the research program would not survive. In part this was the case as the only stable source of revenue for research administration and oversight was from the VA and the amount was calculated as a percentage of VA grant funds received. To correct this problem we expended significant effort in supporting investigators in developing projects and preparing successful grant applications. Our application rate for VA grants doubled and the number of funded grants increased by about eight times over the past two years. In addition, we have added over 20 new investigators (both MD's and Ph.D's) to the Research program through career development type awards addressing the severe problem we had with lack of recruitment into the

Organization. The efforts by the research management team resulted in a significant number of VA grants and career development awards coming to the West Los Angeles VA Medical Center. The new recruits as well as our established staff span expertise in almost every discipline – from laboratory research to clinical trials to health services delivery research. This group is now poised to meet the vision I discussed earlier.

Conclusions

The Research program we inherited was in a state of crisis and collapse. As indicated in this presentation, my research staff and I have made substantial progress in resolving the most severe issues facing the program. Further persistence and determination will result in resolution of remaining ones.

In addition to what we have done, there are certainly other opportunities to improve safety as well as informed consent in human research. Significant issues remain in human research here and around the world while there is an explosion of new therapeutics emerging from academia and industry. Economic issues will push for rapid and efficient performance of human research while safety and informed consent require judicious and careful review and oversight. The VA has both the opportunity and the responsibility to lead the way in ensuring that this enterprise results in therapeutic advances in such disorders as diabetes, heart disease, mental health disorders and cancer without harm to those who participate in testing of new agents and procedures.

To perfect processes to meet OPRR standards is one thing. In our view there are other major issues that need improvement. For example, although much effort has been made to simplify the language in informed consent documents to improve understanding we do not actually measure the degree of subject understanding. This point was elucidated in the report on "Institutional Review Boards: A Time for Reform" by Deputy Inspector General George Grob, presented to the U.S. House of Representatives Conference on Government Reform and Oversight, in June of 1998. Other media such as videos and interactive computer programs should be explored for use to improve research subject understanding.

There must be significant education applied to both the research environment and the general public to ensure active and enlightened participation by both parties. Researchers often are not fully vested in participating in the oversight process while the public is concerned about the safety measures in place. We believe that a dialogue should develop that results in communication on a broad scale to ensure that both parties fully participate thus enhancing the process.

Lessons learned at the VA Medical Center should hopefully result in facilitating the dedication of additional resources to promote the development of a safer, more enlightened and productive system for human research. This, in turn, can promote an environment that fosters the discovery of more effective treatments and cures for illnesses that put us all at risk. The conduct of actions to halt all research at the VA Medical Center and to terminate the Multiple Project Assurance Status served only to punish one organization whose difficulties are merely a reflection of those that permeate IRBs on a national level. Mr. Grob's report to Congress in June, 1998, clearly refers to the systemic dimension of the challenges facing organizations that choose to undertake human research.

Mr. Grob further states that the oversight process should "focus less in narrow compliance matters and more on performance issues." I would hope that my presentation described the continued efforts our Research Administration has made towards enhancing the performance of the oversight processes at our VA Medical Center.

Recommendations

1. The VA should develop a national program for training of administrators and investigators in human research issues.
2. Headquarters needs to develop policy and procedure providing clear guidance on how Medical Center research departments obtain funds to support oversight of projects that are performed at the VA but not funded by the VA.
3. The VA should provide national leadership on developing improvements in informed consent as well as creating the dialogue with the public on importance, performance and safety of human research.
4. Increased resources should be provided to OPRR so that they would be able to provide support and direction with more timely communication and site visits. The lack of resources at OPRR and their inability to provide direct inquiry has also been cited by Mr. Grob in his 1998 report to Congress.

**STATEMENT
OF
KENNETH W. KIZER, M.D., M.P.H.
UNDER SECRETARY FOR HEALTH
DEPARTMENT OF VETERANS AFFAIRS
ON
OVERSIGHT OF RESEARCH IN THE
VETERANS HEALTH ADMINISTRATION
BEFORE THE
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
AND THE
SUBCOMMITTEE ON HEALTH
OF THE
COMMITTEE ON VETERANS' AFFAIRS
U.S. HOUSE OF REPRESENTATIVES**

APRIL 21, 1999

Mr. Chairmen and Members of the Subcommittees, thank you for the opportunity to appear before you to discuss issues related to the recent suspension of research at the Greater Los Angeles Health Care System (GLAHS), specifically, and oversight of VA's research program, generally.

I want to unequivocally state at the outset that the standards for research conduct within VA are among the highest in the country. VA regulations, as applicable, are as comprehensive as the other 16 federal agencies and are more comprehensive than most agencies that are also bound by regulations governing the conduct of research involving humans.

Research is a very important part of VA healthcare, and while VA's medical scientists are devoted to seeking new knowledge, they are, above all else, committed to patient and research subject safety. VA scientists are expected to abide by stringent ethical principles and rigorous regulatory requirements to ensure the protection of their subjects. Respect for the rights, dignity, and safety of research subjects must be, and is, paramount, and there should be no question that all VA research – human, animal or laboratory – shall

be performed in accordance with the highest standards and shall be overseen by vigorous, independent processes.

Research Suspension at Greater Los Angeles Healthcare System

I have previously conveyed to you the specific problems with human, animal and basic research that led to my March 22, 1999, decision to suspend all research activities at GLAHS. In the interest of brevity, I will not repeat all of that here, but I have provided a reasonably detailed recitation of the facts in attachment 1. In addition, I will summarize some of the key points here.

The problems with the human research program at GLAHS involved violations of VA's regulations and policies, which are designed to protect the welfare of human volunteers. Although VA currently has no evidence that anyone was physically harmed by these transgressions, I expect VA investigators to adhere to high ethical standards, federal regulations and VA policy. Clearly, that did not occur at GLAHS for at least one research protocol.

Because the VA Headquarters Office of Research and Development (ORD) had identified various concerns about the fiscal, personnel and animal aspects of the GLAHS research program during the past two years, when the most recent problems were identified it was decided that an all encompassing suspension of research activities was in order (attachment 2). VA Headquarters viewed the action at GLAHS as a pre-emptive measure that was designed to prevent untoward events from occurring at GLAHS. At the time the order was issued, the concerns related to the Cardiology Department were unknown to me. While this suspension has caused significant disruption, I am fully confident that the research program at GLAHS will resolve its problems and emerge stronger and, more importantly, that all parties will have confidence in the conduct of research at its facilities.

Since the March 22nd suspension order, a new Acting Associate Chief of Staff for Research (ACOS-R) and an Acting Administrative Officer (AO) have been detailed to GLAHS; both are from facilities outside of VISN 22. They, along

with VISN management and the VHA Headquarters ORD, are addressing many of the immediate issues that led to the suspension or issues that have been identified since the initial action.

Individual research projects requiring reassessment for human, animal or biohazards concerns are being reviewed by appropriately and legally constituted review panels that have replaced the previous GLAHS groups. I am pleased to report that virtually all animal and non-human/non-animal projects with biosafety concerns have now been appropriately re-reviewed and are once again operational and enrolling new subjects.

With respect to research involving human subjects, a number of important administrative actions must occur before these projects can resume or new projects be initiated. Because of the deactivation by the Office for Protection from Research Risks (OPRR), Department of Health and Human Services (HHS), of the GLAHS Multiple Project Assurance (MPA-1087), GLAHS has had to establish administrative and review mechanisms that provide HHS, VA and other funding sources with the assurance that its human subjects research is conducted in accordance with applicable regulations and policy.

Specifically, GLAHS is negotiating an Inter-Institutional Agreement with its affiliate, the University of California, Los Angeles (UCLA), which holds its own MPA with OPRR. This agreement will allow HHS grants that are funded to UCLA, but performed at GLAHS, to be reviewed by UCLA's Institutional Review Boards (IRBs). Additionally, GLAHS has had to negotiate a multiple project assurance with VA Headquarters to provide VA with binding assurance for all non-HHS funded human research at GLAHS. IRBs constituted under the MPA with VA are re-reviewing all non-HHS funded human research protocols. For HHS-funded human studies at GLAHS, each investigator for each study will submit a Single Project Assurance to OPRR in accord with the terms of the MPA deactivation. These actions are ongoing, and it is VA's hope that the GLAHS research program will be fully stable by the end of April.

Existing VA Protections for Human Research Subjects

Numerous regulations and policies govern the conduct of VA research involving human volunteers. In fact, VA policies and regulations exceed those required by other government agencies, including HHS.

Federal Regulations

This past weekend, a distinguished gathering of scholars paid tribute in Charlottesville, Virginia, to the 20th anniversary of the *Belmont Report*, the genesis for federal requirements to ensure the ethical conduct of research involving humans. These federal regulations, and by extension VA's, derive from the Federal Policy for the Protection of Human Subjects (often referred to as the "Common Rule," 56 FR 28003). Seventeen federal agencies, including VA, are co-signatories to the Common Rule.

VA has incorporated the Common Rule into its own regulations at 38 CFR 16. VA is legally bound to adhere to the regulations articulated within 38 CFR 16, which includes detailed descriptions of informed consent and the structure and responsibilities of Institutional Review Boards (IRBs). (Some VA facilities have adopted the terminology Human Subjects Subcommittees [HSSs] for this entity.)

I note that it is important to recognize that VA considers all research at a VA facility as VA research, even if the funding is from non-federal sources. Thus, any research, at VA, regardless of the funding source, is subject to the regulatory requirements of the Common Rule and VA's additional protections. VA's blanket pledge of full and equal protection for all human subjects exceeds that of even some institutions who hold MPAs with OPRR. Of note, OPRR has identified unchecked human experimentation at a broad range of venues, including some colleges and universities not receiving federal research funds and some physician, dental and psychotherapist practices. None of this involves VA facilities.

For human studies conducted at a VA facility in support of a new drug or device application to the Food and Drug Administration, the human studies component also comes under the authority of FDA regulations for the protection of human subjects in research (21 CFR 50 and 21 CFR 56). Because 38 CFR 16 regulates all federally sponsored research at VA – and because 21 CFR 50 and 21 CFR 56 cover all VA research in support of a new drug or device application – when VA researchers are engaged in research that supports a new drug or new device application, the researchers must comply with both sets of regulations.

VA and FDA are partners in a memorandum of understanding that enhances the communications between FDA and VA with respect to a number of FDA requirements. In particular, FDA has agreed to notify VA medical center directors of investigative findings relating to a particular study, and advise VA of any violations resulting from investigations into the performance of clinical investigators or Human Studies Subcommittees (HSSs/IRBs) associated with VA.

Finally, VA has gone further in protecting human research subjects than is provided by either the Common Rule or FDA regulations. Despite repeated calls that the federal government address the issue of compensating research injuries, VA is the only agency that has extended its regulations (38 CFR 17.85) to provide for compensation to persons injured as a result of participation in VA research.

VA Policies

In 1992, shortly after the establishment of the federal Common Rule, VA issued a revised policy and incorporated it into our policy manual, M3, Pt.1, Ch.9, "Requirements for the Protection of Human Subjects".

Chapter 9 incorporates the provisions of the Common Rule (38 CFR 16), and FDA regulations (21 CFR 50 and 56). In addition, Chapter 9 explains how

the provisions of these regulations are to be implemented in the specific context of research at VA medical centers.

Just as VA's regulatory requirements exceed those under the Common Rule, VA policy (M3, Pt. 1, Ch.9) exceeds the policy and regulatory requirements of other entities. For example, the Common Rule is relatively silent on the issue of informed consent in persons with impaired decisionmaking capacity, only pointing out the possibility of consent by a legally authorized representative. In contrast, M3, Pt.1, Ch.9, sec.12 is devoted entirely to "Research on Human Subjects with Surrogate Consent". It describes in explicit detail the specific conditions under which an investigator may seek surrogate consent for an individual with impaired decisionmaking capacity.

Finally, because VA has a large program in cooperative trials for the study of new drugs, therapies and devices, the VA Cooperative Studies Program developed detailed guidelines, "Cooperative Studies Program: Guidelines for the Planning and Conduct of Cooperative Studies," in 1997. A major part of these guidelines is devoted to describing the requirements for protocol review and informed consent. These guidelines derive from 56 FR 280003 (the Common Rule), 38 CFR 16, and the VA policy manual M3, Pt.1, Ch.9.

Enhancing Oversight of VA Research

VA oversight of its human subjects research is equal, or in many ways better, than oversight by non-VA research institutions. Indeed, a broad series of initiatives to assess the systemic nature of any deficiencies, or lack thereof, have been underway for some time. I am also initiating two new, broad-based initiatives that will position VA as the clear leader in ensuring that its research is of the highest ethical and legal caliber.

Existing Efforts

Before describing the two new initiatives, I would like to briefly highlight six programs that demonstrate that VA has been cognizant of the need to exercise due diligence in monitoring the conduct of VA research that involves human subjects.

- In 1995, the VHA Office of Standards in Human Research (part of ORD) was formed and located at the Portland VAMC. Since its inception, the office has conducted 12 random site visits to medical centers across the country. Site visit teams reviewed: IRB records, informed consent documents, all local policies and procedures in place to implement national requirements under the Common Rule, FDA regulations, and VA manual M3, Pt.1, Ch.9. In addition, medical center directors, chiefs of staff, associate chiefs of staff for research, and researchers were interviewed. At the sites visited, the site visit teams found failures in documentation, but no instance of violation of any patient's rights or health and well-being. Likewise, they found no instance of either willful or intentional misconduct.
- Since 1975, the VHA Cooperative Studies Program Human Studies Committees have conducted performance site visits and they currently assess 12 sites per year. Along with audit activities, the Committees also interview research volunteers regarding their experience as a research participant, including an assessment of the subjects' informed consent.
- The VA Cooperative Studies Program conducts 45 audits per year, on average, of its drug studies at selected performance sites. These audits began in 1997.
- The VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center is FDA-approved for packaging, dispensing, and monitoring pharmaceuticals and devices for drug trials. The

Coordinating Center audits each drug trial at each study site at least once during the life of the trial; these audits began in 1975.

- ORD conducts approximately six site visits per year of its research centers for evaluation of performance and determination of continued funding. It also investigates allegations of variations from prescribed research policies.
- The Nuclear Regulatory Commission conducts site visits of its low-level radiation licensees (including VA medical centers and research facilities) every three years. When human studies are conducted under the license, NRC site visitors review human ethical standards and compliance.

New Initiatives

Clearly, the most important question facing the VA research program is whether the problems at GLAHS are an isolated occurrence, or do they represent a more serious endemic problem within the VA research system?

I have no evidence that the latter is the case. Moreover, I am pleased at the level of Headquarters oversight that ORD has to date initiated or has underway. Nevertheless, I believe the time has come for more comprehensive and systematic efforts at overseeing research programs. Veterans, the Congress, and VA need independent and routine assurance that VA research is conducted ethically, legally, safely and with integrity. I have, therefore, directed the implementation of two major new initiatives:

- establishment of an independent Office of Research Compliance and Assurance, and
- publication of a request for proposals to establish an external accreditation program for VA research, in general, and VA research involving human subjects, in particular.

Office of Research Compliance and Assurance (ORCA)

First, I am establishing a new office, the Office of Research Compliance and Assurance (ORCA), which shall report directly to the Office of the Under Secretary for Health. This office will be in several ways similar to the Office of the Medical Inspector (OMI). ORCA's mission will be to provide VHA with the assurance that research conducted by our scientists is done with maximal regard for issues of: 1) human and animal subject protection; 2) safety of laboratory personnel (chiefly chemical and biological, and in consultation with the National Health Physics Program, radiological); and 3) research integrity (e.g., conflict of interest, scientific misconduct, research ethics).

ORCA will operationalize its functions in a manner similar to that of OMI, but, in contrast, a majority of ORCA's compliance officers will be based in field offices located across the country (up to six) to: 1) enhance the ability of ORCA to rapidly respond to or consult on emergent incidents, and 2) facilitate a reduction in the costs of routine inspections.

I want to particularly emphasize that ORCA will be an independent, objective and unbiased entity in its compliance and oversight activities.

External Accreditation

Today, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) provides the public assurance that JCAHO-accredited healthcare organizations meet or exceed minimum quality standards. All VA medical treatment facilities participate in JCAHO inspections. Similarly, the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC) inspects and accredits research animal facilities in the United States and abroad. VA animal laboratory facilities, along with scores of private-sector sites, are inspected every three years by AAALAC. No comparable mechanism exists for institutions conducting research involving human research. VHA intends to address this vacuum.

In the very near future, VHA will publish a notice that seeks to identify an external entity to serve as an accrediting body for its research programs. The highest priority will be for the selection of an accrediting body to perform routine site visits (e.g., every three years) for the purpose of reviewing the performance of the IRB/HSS systems and other such processes at VA medical centers and research institutions. Through this notice, VA will become the driving force to establish both an accreditation entity and an accreditation process for research involving human subjects similar to that performed by AAALAC for animal research. No such entity currently exists, and thus, VA will clearly be traversing new ground with this effort.

That such an entity is overdue is now without question in my mind. In March 1999, the HHS Regional Inspector General who was responsible for a 1998 HHS Office of Inspector General review of IRBs stated, "...as a matter of public policy, the time is right to foster a system of accrediting IRBs. I believe that FDA and NIH should collaborate in determining what they can do to stimulate this development, and I think they should do it with some sense of urgency." Moreover, accreditation was recommended in 1983 by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. I am particularly pleased that VHA will provide the leadership whereby, at last, nationwide accreditation in this area could be achievable. I hope other federal agencies will join with VA in this effort.

Conclusion

Today, as in the past, the research enterprise of the United States is the envy of the world. It has produced extraordinary advances in medical care and many other areas. There is no dispute that such advances depend on the participation in research of our relatives, neighbors, friends and fellow citizens – including men and women who have served in the Nation's armed forces.

I am proud that VA scientists have made more than their fair share of contributions to medical research. But I am more proud of, and grateful for, the

willingness of veterans to afford VA the privilege of participating in the U.S. research enterprise. Having served this country once in the military, veterans' participation in biomedical research again serves the interests of the Nation because research is the cornerstone for increasing knowledge that helps us all. We owe them assurances that their interests will be protected by standards second to none.

While the increasing reports of investigations into VA research at multiple facilities may cast a temporary shadow over our program, I am confident it will do so only briefly. The existing measures and policies in place, combined with our new initiatives, will place VA at the forefront of protecting human research subjects. To maintain the public trust we must all share a vigorous commitment to protect the rights and welfare of those who participate in research protocols. I hope those outside of VA will quickly join our efforts to ensure there are effective checks and balances in place to protect human research subjects.

Again, I appreciate the invitation to discuss these important issues with you, and I will be pleased to try and answer any questions you might have.

Attachment 1**GREATER LOS ANGELES HEALTHCARE SYSTEM:
SUMMARY OF RESEARCH ISSUES**

VHA considers the protection of human and animal subjects and our laboratory employees to be among our highest priorities. Dating to a site visit in September 1996, VHA Headquarters has had concerns about the administration of the Research Service at the West Los Angeles campus (then West Los Angeles VAMC), in particular. This attachment summarizes the concerns identified at GLAHS to date and the current plan to address them.

Financial Issues

In spring 1997, the National Institute on Drug Abuse (NIDA) raised concerns about the financial management of a VA-NIDA collaborative agreement for medication development by the Research Service at the West Los Angeles facility. In May 1997, the Chief Research and Development Officer (CRADO) placed the West Los Angeles Research Service on administrative probation. This history of financial management concerns, coupled with new and historical concerns about administration of human, animal, and bio-safety research (described below), led VHA to suspend all research conducted at GLAHS as of March 26, 1999.

Human Studies

On March 22, 1999, OPRR deactivated its Multiple Project Assurance (MPA-1087) for GLAHS, which encompasses the former VA medical centers at West Los Angeles and Sepulveda, and affiliated clinics. MPA-1087 is the mechanism by which GLAHS assures OPRR that GLAHS conducts its research involving human subjects in conformance with 45 CFR 46. This HHS regulation incorporates 52 FR 28003, also referred to as the "Common Rule" for the protection of human subjects in research and which is subscribed to by 17 federal agencies that fund research involving human subjects.

As permitted under the Common Rule, VA accepted MPA-1087 as its own assurance that VA research at GLAHS was conducted in accordance with federal regulations. Moreover, since VA considers all research, regardless of sponsor, conducted at VA medical centers to be VA research, MPA-1087 covered all human research conducted at GLAHS whether HHS, VA, or any other source funded it. Consequently, OPRR's actions effectively removed all assurance that research involving humans being conducted at GLAHS was in legal and ethical compliance.

OPRR's deactivation of MPA-1087 resulted from the failure of GLAHS to adequately respond since April 1993 to requests by OPRR to change and/or

document procedural and administrative matters related to the way GLAHS conducted initial and ongoing reviews of protocols involving humans. Specific problems cited by OPRR included:

- meetings of Institutional Review Boards (IRBs) (committees that are responsible for the review and monitoring of human studies protocols) that did not meet with a quorum of voting members as required by 45 CFR 46;
- the absence from IRB membership roles of appropriate community/patient representatives;
- Data Safety Monitoring Boards had not been established by GLAHS as requested by OPRR in 1994;
- inadequate procedures for continuing review of ongoing projects;
- failure to implement policy changes recommended by OPRR; and
- the use of "expedited review" procedures by IRBs to approve research studies with greater than minimal risk in contradiction to the requirements of 45 CFR 46.

Most of these infractions occurred at the West Los Angeles campus of GLAHS. Since the merger of West Los Angeles and Sepulveda, both campuses have operated under the same MPA. Thus, the deactivation of the MPA-1087 affected both campuses equally.

Animal Studies

Both the West Los Angeles and Sepulveda campuses have problems with their animal programs, but those at Sepulveda are more serious.

A report of the Institutional Animal Care and Use Committee (IACUC) of the GLAHS Research and Development (R&D) Committee found that the laboratory animal care facilities at the West Los Angeles campus were acceptable. A site visit by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) to the West Los Angeles animal care facility found that the occupational risk of animal handlers had not been assessed properly and is requiring changes in policies and procedures. AAALAC's final report on West Los Angeles is pending. It is likely AAALAC will recommend additional minor policy and procedures changes and place the West Los Angeles campus under restriction until it is satisfied that the problems have been rectified. Additionally, in April 1998, the Medical Research Service, Office of Research and Development (ORD), VHA Headquarters, expressed its concern to the Associate Chief of Staff for Research (ACOS-R) at the West Los Angeles facility about the lack of progress to correct infrastructure and leasing deficiencies related to building 337 and about attempts to pressure members of the Institutional Animal Care and Use Committee (IACUC) inspection report.

Although requesting a response within seven working days, none has been received.

At the Sepulveda campus it is anticipated that AAALAC will place the animal facility on probation for multiple program deficiencies related to the occupational risks of animal handlers and specific problems with animal housing, such as temperature, humidity and crowding.

Non-Human/Non-Animal Studies

This classification covers virtually all basic research. The VHA Headquarters Emergency Management Site Visit Team that visited GLAHS on March 25-26, 1999, found serious deficiencies in the bio-safety program at GLAHS, in particular at the West Los Angeles campus:

- Required reviews of research protocols for bio-safety issues were done by a junior investigator without appropriate expertise for all hazards being reviewed;
- No minutes of the Bio-Safety Subcommittee (a subcommittee of the R&D Committee) documented any kind of bio-safety review. The reviews existed only in draft form in the reviewer's laptop computer;
- The Bio-Safety Subcommittee accepted verbal reports from the reviewer without written documentation of review;
- Bio-Safety Subcommittee minutes are more than six months in arrears—i.e., over six months of minutes are missing. R&D Committee minutes repeatedly note that Bio-Safety Subcommittee minutes are missing, but no action had been taken to correct this problem. Since the R&D Committee is supposed to accept committee reports as final approval, none of the bio-safety studies has had proper approval for months.

The Emergency Management Site Visit Team found no significant problems at the Sepulveda campus with respect to bio-safety issues.

Reinstatement of Research at GLAHS

A full Recovery Plan for research at GLAHS has been developed by VHA Headquarters, Office of Research and Development and Veterans Integrated Service Network 22.

Phase 1

- The GLAHS is notified on March 22, 1999 that all research activities will be suspended on March 26, 1999.
- Research suspended encompasses all human, animal, non-human/non-animal research at the West Los Angeles, LA Outpatient Clinics, and Sepulveda campuses of GLAHS. Exceptions are made for human and

animal studies whose suspension could place research subjects at risk if respective studies were stopped abruptly.

Phase 2

- Total research suspension in effect and all VA research funds are withdrawn on March 28, 1999.
- On-site Emergency Management Team from VA Headquarters is on-site at West Los Angeles and Sepulveda on March 25-26, 1999.

Phase 3

- Full-scale site visit team at GLAHS to assess status of entire research program April 5-9, 1999.

Phase 4

- Partial research suspension in place (expected April 1999 after review of site visit report); external management team in place (ACOS-R and Administrative Officer detailed from other facilities). If the site visit team identifies specific components of the research program that are functioning properly, legally, and ethically, it may recommend to the Under Secretary for Health that discrete components of the research program should be re-instituted.

Phase 5

- Research suspension removed partially, but probation in place (expected action of April-May 1999); interim management team (i.e., temporary ACOS-R and Administrative Officer) identified.
- Re-constitution of the research administrative and oversight functions completed;
- Probationary period and HQ monitoring instituted.

Phase 6

- Suspension removed, probationary period in place (1999); expected minimum duration May 1999-May 2000;
- National search for new, permanent ACOS-R.

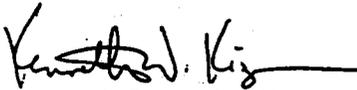
Phase 7

- Probationary period in place to extend one year after appointment of the new, permanent ACOS-R (likely May 2000-May 2001).

**Department of
Veterans Affairs****Memorandum****Date:** MAR 22 1999**From:** Under Secretary for Health (10)**Subject:** Research Program at VAMC West Los Angeles**To:** Acting Director, VA Greater Los Angeles Health Care System (691/00/151)**cc:** Chief Network Officer
Chief Research and Development Officer
Network Director, VISN 22

1. This memorandum officially notifies you that the Veterans Health Administration (VHA) joins the Department of Health and Human Services (HHS), Office for Protection from Research Risks (OPRR), in suspending research activities at the West Los Angeles VA Medical Center. However, please note that this memorandum is directed toward all research activities conducted at West Los Angeles VAMC – both research involving humans, as well as research involving animals. This suspension is broader than that encompassed by OPRR's letter of deficiency. Additionally, because the Sepulveda facility is encompassed by HHS's Multiple Project Human Subjects Assurance (MPA #M-1087) to West Los Angeles VAMC, this suspension includes research at the Sepulveda campus and all other facilities in the VA Greater Los Angeles Health Care System (HCS).
2. As you are aware, VHA's Office of Research and Development (OR&D) conducted a site visit at VAMC West Los Angeles on March 17-18, 1997. As a result of observed deficiencies, the Research Service, VAMC West Los Angeles was placed in a probationary status in May 1997. The status of this probation was reviewed in February 1998. OR&D has worked with facility management to alleviate specific problems with human studies and reviewed the facility's responses to deficiencies. Nevertheless, it is clear to me that the West Los Angeles VAMC management, including research administration, has failed to correct deficiencies in fiscal and personnel management, and overall management of the research program, including a lack of adherence to research policies concerning R&D committee functions, as well as human and animal studies assurances. This failure is underscored by OPRR's decision to deactivate MPA #M-1087.
3. On March 16, 1999, the Chief Research and Development Officer notified you of his continued dissatisfaction with the performance of West Los Angeles VAMC research management, and the OR&D has scheduled another extensive site visit review of the entire research program.

4. The action to suspend research activities at Greater Los Angeles HCS should be seen as a pre-emptive measure that reflects the local institution's inability to resolve with NIH its probationary status, as well as the inability to address OR&D's concerns about the problems it has identified. We recognize that there currently is no evidence to suggest any actual harm to either human or animal research subjects. However, we consider the Greater Los Angeles HCS management's response to the research program probation to be wholly unsatisfactory. The lack of adherence to research policy and operational requirements is a very grave matter. Regrettably, facility management's unresponsiveness now adversely affects individual investigators in the Greater Los Angeles HCS. It also jeopardizes the public's perceptions of VA's entire research enterprise even though no other VA facilities are in probationary status.
5. By close of business March 25, 1999, local research management must identify any ongoing research program for human beings or animals, which if suspended or otherwise interrupted, would cause potential harm to those research subjects. These projects should be submitted to VHA Headquarters, OR&D for immediate review and disposition.
6. OR&D will work with the VISN leadership to identify an interim research management team to assume operational responsibilities for addressing the most immediate research management deficiencies. No research project may continue beyond close of business March 26, 1999, unless it is explicitly approved by OR&D.
7. It is with deep disappointment that this action is taken, and it is my expectation that you will move immediately to fully address the problems identified by OPRR and by OR&D.



Kenneth W. Kizer, M.D., M.P.H.



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Testimony of

**Eric M. Meslin, Ph.D.
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**Before the
Subcommittee on Oversight and Investigations and the
Subcommittee on Health
Committee on Veterans Affairs
U.S. House of Representatives
Cannon House Office Building, Room 334
April 21, 1999**

Good morning Mr. Chairman and members of the Subcommittee. I am Eric M. Meslin, Ph.D., Executive Director of the National Bioethics Advisory Commission (NBAC). I am pleased to appear before you this morning to describe the recommendations NBAC recently made in its recent report on *Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity*. The report is available on the Commission's website (www.bioethics.gov), and the Executive Summary was published in the *Federal Register* on February 19, 1999. The report was completed and published in late December 1998, and forwarded to the President on January 8, 1999—as required by our Executive Order. Since I have made copies of this report available to the subcommittees as part of my written testimony, with your permission I will briefly summarize NBAC's recommendations.

Mr. Chairman, as you are aware, there have been previous efforts to extend additional regulatory protections for research involving individuals with mental disorders, but these efforts have not been fully successful. In the late 1970s the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission), studied the need for special protections for research subjects with mental disorders in a report on *Research Involving Those Institutionalized as Mentally Infirm*. The Department of Health Education and Welfare proposed regulations in 1979, but these were never adopted.

NBAC decided to study this topic as part of its overall mission to advise both the National Science and Technology Council, and other government entities on appropriate

policies, guidelines, and other instruments addressing the bioethical issues arising from research on human biology and behavior.¹ NBAC examined this topic because of the special needs of these human subjects—including the need for more research—but also because of the weaknesses in federal regulations that have persisted for the past two decades. Several highly publicized incidents involving research subjects in this vulnerable population were also brought to the NBAC's attention.

During its 18-month study, NBAC heard testimony at 13 separate meetings from members of the public, scientists, former research subjects, their families, and others; obtained nearly 120 public comments during a 45-day comment period on a draft report; reviewed commissioned papers from leading experts in law, medicine, psychiatry, and ethics; and reviewed a small sampling of research protocols in this field.

NBAC found that important progress has been made by the nation's scientists on the cause and treatment of mental disorders, with more opportunities likely to emerge; that the scope of research is expanding; and that the research environment has become far more complex, involving both a larger societal investment and a greater role for the private sector.

NBAC concluded, however, that in addition to the existing Federal Policy for the Protection of Human Subjects, "research involving subjects with mental disorders that may affect decisionmaking capacity should be governed by specific further regulations."

¹Exec. Order No. 12,975, 60 Fed. Reg. 52,063 (1995), reprinted as amended in 42 U.S.C. §6606 (1997).

As Dr. Harold Shapiro stated in his letter to the President transmitting the report, "While current U.S. regulations note the need to ensure ethical treatment of human research subjects with mental disorders, they provide no specific guidance for IRBs and investigators regarding vulnerable subjects... We believe that this state of affairs is not satisfactory, and that additional federal protections are necessary."

NBAC made 21 recommendations. Many of the Commission's recommendations are non-controversial, and should enjoy broad support. For example: research should not target people with mental disorders when research can be done with other subjects (Recommendation 3); researchers should describe the risks in studies to IRBs so that IRBs can make an informed risk/benefit assessment, a determination that is especially important when the studies involve placebo controls, symptom provocation, or rapid medication withdrawal (Recommendation 4); a subject's objection to participation should be heeded even if he or she is confused or is incompetent (Recommendation 7); and that IRBs should ensure that researchers establish and maintain ongoing communication with the subjects family and friends (Recommendation 17).

Some of the other recommendations will likely be seen by researchers as too restrictive of research, and by those concerned with the rights of subjects as too permissive. For example, NBAC's recommendation that where research involves greater than minimal risk, IRBs should often require researchers to obtain an independent assessment of the subject's capacity to consent (Recommendation 8) may be considered too great an imposition on researchers and institutions, while some advocates for patients' rights

might have hoped to see this recommendation go further, requiring that all research subjects, regardless of the level of risk in a study, be assessed for their capacity. Some will no doubt consider NBAC's recommendations that subjects who are capable of consenting can, under certain conditions, give a "prospective authorization" to their future involvement in research (Recommendation 13) an important method for permitting competent persons to express their wishes for participation in studies in the future when they are no longer able to express their wishes, others may find that this recommendation permits people to be enrolled in research without their express informed consent.

NBAC was persuaded that for research involving greater than minimal risk but that does not hold out the prospect of any medical benefit, subjects could be involved only under the most stringent conditions. In particular, NBAC recommended that the Secretary of Health and Human Services convene a Special Standing Panel to review these protocols at the national level (Recommendation 2). This Standing Panel would include members representing the diverse interests of potential subjects, the research community and the public. This Panel would provide a national, and publicly accountable review mechanism for research. It would be charged with developing guidelines that could be used by local IRBs. NBAC recommended that all federal agencies subject to the Common Rule use this panel, and that a study of its effectiveness be completed within five years.

The NBAC report identified, where possible, those who should be responsible for implementing the recommendations. While NBAC did not single out the Veteran's Administration in its recommendations, NBAC intended for all agencies subject to the

"the Common Rule," including the VA, and others responsible for human subjects protection to consider the Commission's recommendations.

NBAC proposed a number of recommendations for regulatory reform, but it did not take a position on whether these reforms would best be accomplished through changes in the Common Rule, or through the adoption of a new Subpart in the Code of Federal Regulations. More importantly, the commission made clear its belief that some of these changes could be implemented voluntarily at the local level, italicizing the following statement in the report: *Regardless of which regulatory route is selected, NBAC encourages researchers and institutions to voluntarily adopt the spirit and substance of these recommendations.*

Like all agencies subject to the Common Rule, the VA has recently received a copy of NBAC's report. It is my understanding that all federal agencies responsible for conducting research involving human subjects will be reviewing the report and providing comments to the National Science and Technology Council by the end of May. NBAC is pleased that the agencies are reviewing its report and recommendations stands ready to offer any advice or assistance.

The recommendations provide both a set of requirements that NBAC believes must be satisfied in all research protocols involving persons with mental disorders, and several additional or optional protections that may be considered, as appropriate, in particular

circumstances. Taken together, these recommendations would both enhance existing protections and facilitate broad public support for continued research on mental disorders.

Mr. Chairman, the subject of this hearing comes at an important time in the history of human subjects protections in this country. The opportunity exists to identify and correct deficiencies in the present system, but also to plan for how best to build the system as we move into the next century. In NBAC's view, the enhanced protections recommended in its report will promote broad-based support for further research by engendering greater public trust and confidence that subjects' rights and interests are fully respected.

I would be pleased to discuss any of the report's recommendations in more detail, and of course, NBAC would be pleased to work with you and your subcommittee as you continue to address these important issues.

Thank you Mr. Chairman.

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TESTIMONY
OF THE
AMERICAN PSYCHIATRIC ASSOCIATION
on
SUSPENSION OF MEDICAL RESEARCH AT THE
WEST LOS ANGELES AND SEPULVEDA VA MEDICAL FACILITIES
before the
SUBCOMMITTEES ON OVERSIGHT AND HEALTH
of the
VETERAN'S AFFAIRS COMMITTEE
U.S. HOUSE OF REPRESENTATIVES

Presented by
Paul Appelbaum, M.D.

April 21, 1999



Mr. Chairman, I am Paul Appelbaum, MD, testifying on behalf of the American Psychiatric Association (APA). The American Psychiatric Association is America's oldest medical specialty society, representing more than 42,000 psychiatric physicians nationwide. I serve the APA as its Vice-President Elect and Chair of its Ethics Appeals Board, and I am also Professor and Chair of the Department of Psychiatry at the University of Massachusetts Medical School. My research over the last two decades has focused on legal and ethical aspects of medical practice, including informed consent to medical research.

West Los Angeles Veterans Administration Health Care Center

We welcome the Committee's interest in insuring that the rights of veterans in VA Medical Centers are protected, and we look forward to working with the Committee in their effort. Certainly, the reported lapses and abuses at the West L.A. Medical Center are very serious. We believe the interests of patients, particularly veteran patients come first. In our pursuit of more effective treatments for individuals suffering from illness and disease we must never compromise the rights of patients. Subtly coercive techniques to obtain consent are unacceptable, as are inadequate disclosures of information to potential subjects and failures to insure that patients truly understand the consent documents they sign. Simply put, if research cannot be performed without violating the rights of participants, it should not take place at all.

We must be particularly careful to protect individuals participating in research whose illnesses may impair their decisionmaking ability, thus reducing their capacity to protect themselves. In these cases additional safeguards are required.

Finally, scientists cannot produce needed breakthroughs in medical research and treatment for patients without the trust and support of both patients and the public. Medical research efforts must maintain the highest standards of integrity and research participant protection.

The most troubling concerns about research at the VA in West Los Angeles involved cardiology patients and specifically on abuses of the requirements for informed consent and patient protection. It was in cardiology that patients were subject to research without consent and indeed over their opposition. This is unconscionable, especially since the research was classified as medium to high risk. Finally, one of the patients who consented to the research may not have fully understood that he was participating in a research project, and it is not yet clear if his death was associated with the treatment he received in the research project.

While the other violations raised by OPRR do not appear to have resulted in any harm to patients or enrollment of patients in research without their informed consent, they are also of great concern, especially since these violations went uncorrected for a period of years. If procedural safeguards are not diligently followed, the risk to participants in research greatly increases as does the risk that patients will not actually be informed of and or understand the nature of their involvement in research projects.

Given the lapses and abuses at the West L.A. Veterans Medical Center it is of course important to reiterate that patients have the right to and must exercise informed, voluntary, non-coerced

consent before they enroll in any research projects. It is even more disturbing that these events occurred in government financed and operated medical centers. The federal government and the American people owe a special debt of gratitude to our veterans and thus there should be a special effort to insure that they are not harmed and their rights are fully respected.

As the Committee proceeds with its work to insure that the rights of veteran patients are protected, I hope your efforts will include providing additional training and sensitization of investigators and the encouragement of extra levels of protections in the informed consent process. Also, I believe it is important to determine to what degree the violations at West L.A. are isolated incidents or if they indeed are indicative of more widespread problems and a pattern of conduct that needs remediation. I also was particularly distressed and concerned that needed corrective actions were not taken more rapidly.

But we must not respond without cautiously studying the full consequences of our actions. We must carefully craft these protections so as not to unnecessarily impinge on the development of new treatments of these terrible disorders. Otherwise, desperately needed new treatments for patients may be lost.

Scope and Importance of Research on Conditions that May Impair Decisionmaking Capacity

Because of the traumas associated with combat, as well as the relative age of the veteran patient population, many veteran patients experience impaired decisionmaking. This Committee is undoubtedly well aware of the suffering associated with disorders that may impair decisionmaking, including psychiatric, neurological, and other medical disorders. A recent World Health Organization report noted that of the ten leading causes of disability in the world, five were psychiatric conditions: unipolar depression, alcohol use, bipolar affective disorder, schizophrenia, and obsessive-compulsive disorder. The direct and indirect costs of mental illness and substance abuse in the United States totaled more than \$313 billion in 1990. More than 4 million Americans suffer from Alzheimer's disease, the leading cause of dementia in the elderly. With the number of persons over 65 years of age expected to double by the year 2030, the prevalence of dementia and its costs for families and society will grow accordingly.

Effective research is the key to more effective treatment of these disorders and to the reduction of the suffering they cause. The introduction of the first effective treatments for schizophrenia and other psychotic disorders in the 1950s permitted, for the first time in history, the long-term treatment of persons with these disorders in the community, rather than in institutions. More recently, the development of a newer generation of antipsychotic medications, with greater efficacy and fewer side effects, has been estimated to have yielded savings of \$1.4 billion per year since 1990. Lithium treatment for bipolar disorder, introduced in this country in the 1960s, has restored tens of thousands of patients to functional membership in society, at an estimated cost savings of \$145 billion. None of these advances would have been possible without the assistance of persons suffering from these disorders, who volunteered and with informed consent agreed to participate in trials of the effectiveness of these new medications. These advances have greatly reduced human suffering and allowed many individuals and their families to lead healthy productive lives.

The future for research on disorders affecting the brain is also a bright one. New imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), promise advances in our ability to identify regions of the brain associated with cognitive and affective disorders. In addition, precise characterization of the shape of neurotransmitter receptors in the brain is permitting the design of drug molecules targeted specifically at enabling disordered brain systems to function properly. These developments and future research efforts offer the promise not only of dramatically improving current treatment for patients and but also of developing medications for currently untreatable conditions.

Because our brains are truly unique in nature, volunteers drawn from patients afflicted with these illnesses are essential for progress to be made. Moreover, unless research is to be restricted to the mildest forms of the disorders—which will limit our abilities to treat those people whose suffering is greatest—persons whose cognitive capacities are impaired will need to be involved.

Protecting Persons Participating in Research Who May Have Impaired Decisionmaking

Because V.A. Medical Centers serve a disproportionately high number of patients with impaired decisionmaking capacity, we must be particularly sensitive as well as careful to insure that veteran patients make a fully voluntary and informed decision concerning their possible enrollment in research projects.

The American Psychiatric Association endorses as its starting point in addressing the complexities of this area the dual importance of two key principles: 1) minimizing risk to those persons who volunteer to participate in research studies; and 2) maximizing participants' knowledge of what their involvement will entail, so that they can make a meaningful decision regarding participation. Were it not for the willingness of persons suffering from psychiatric, neurologic, and other disorders to join research projects, as I noted previously—often with the critical support of their families—no progress would be possible in the treatment of these disorders. Unless potential participants can be assured that their interests are being taken fully into account, the basis of trust on which the process depends will crumble.

How can these principles be implemented? First, we must recognize that some populations evoke greater concern, and may require greater efforts at protection, than others. This is not to suggest that attention should not be paid to protecting the interests of all persons recruited into research projects. Inadequate information about what a project entails or confusion about how research participation may affect one's own care can impair the ability of even the most capable person to guard his or her own interests. Thus, continuous improvement in the consent process and ongoing monitoring of its effectiveness is required for all medical research.

There is no question however, that some potential participants in research will have a harder time than others grasping what is involved. Defining this group is no simple matter. Reflection quickly reveals that potential problems are not limited to persons with psychiatric and neurological disorders. Other medical conditions—such as stroke, aging, infection, lack of oxygen in the bloodstream, and metabolic imbalances—can impair thinking and compromise decision-making abilities. Even something as ubiquitous in medical settings as physical pain can

distract a person from attending to and assimilating information necessary for a knowledgeable consent.

Thus, if we are to fulfill our duty toward those participants most in need of protection, we cannot limit the scope of our attention only to persons with psychiatric or neurological disorders. Nor is the presence of a psychiatric or neurologic diagnosis alone sufficient to place a person in a high-risk group for difficulties in the consent process. Research has shown that the decision-making abilities of many persons with mental disorders are no different from those of comparison groups free of such disorders. To classify all persons with mental disorders as cognitively or emotionally impaired would revive the stereotypes against which we have been struggling for so long. Rather, if resources are not to be wasted, effort diffused, and stigma promoted, individualized judgments must be made about the likelihood of decisionmaking impairment in individuals participating in research projects. In our current regulatory system, those judgments are the responsibility of the Institutional Review Board (IRB). When the presence of such impairment is likely, additional safeguards should be required.

Some of the recent recommendations of the National Bioethics Advisory Commission, (NBAC), and others, may be helpful here. These include appointing persons particularly knowledgeable about and concerned with cognition-impairing disorders to IRBs reviewing studies using populations who are likely to manifest such impairment; requiring justification for the use of such populations to ensure that less vulnerable groups could not be recruited instead; and paying greater attention to the decisionmaking competence of individual subjects. Moreover, we would encourage IRBs—in higher risk studies of all kinds—to abandon their reliance on paper reviews and develop mechanisms for the direct monitoring of patient protections (e.g. assessments of the efficacy of the informed consent process).

The second focus for implementation of the principles that we suggest are central to protecting persons in research is that additional safeguards for subjects should be tailored to the needs of particular populations, rather than being applied on a blanket basis. This is consistent with the conclusions of the recent National Institutes of Health Panel Report on Research Involving Individuals with Questionable Capacity to Consent. Specifically, as the likelihood of cognitive impairment increases in a given population, and as the potential risks associated with research participation rise, greater attention should be given to additional protections for research participants. To do otherwise is to inappropriately burden medical research with the costs of protections that are unlikely to benefit the very people who they are intended to assist.

What is key, we believe, is to recognize that the presence of some degree of cognitive or emotional impairment does not in and of itself mean that potential participants cannot give an adequate informed consent to research. It is an understandable first response to say that any research on individuals with these disabilities should be ruled out, but this would be a tragic mistake of immeasurable negative consequences to those most in need of research advances. Such a step both is unnecessary in protecting these individuals and also would cause promising research on a wide variety of conditions to grind to a near complete halt.

Individuals with cognitive impairment may, however, require special efforts at education, with particular emphasis on ascertaining that they understand and appreciate the implications of

research participation. Psychiatric researchers have already begun to employ some of these techniques for protecting patients' interests, but we would like to see them applied on a much broader scale. These approaches include screening suspect populations for decisionmaking impairment; testing subjects after information disclosure to insure that they have understood what is involved in research participation; utilizing waiting periods between information disclosure and entry into the study to minimize the possibility of situational coercion, allowing potential participants to reflect on their desires and to discuss options with family members and other advisers; and providing extended educational sessions, including family members and persons who already have participated in the study in question, to maximize potential participants' grasp of what it means to enter this research project.

Widespread adoption of these procedures, we believe, would provide an important extra degree of protection for patients. By no means is this an exhaustive list of possibilities. It is crucial, though, for each research project to be considered on its own with an individual determination made in each particular case.

Third, mechanisms with appropriate safeguards are required for permitting persons who lack decision making capacities—either because of age or illness—to participate in research projects. Failure to provide such mechanisms would mean no clinical research could take place on many illnesses and indeed virtually all illness affecting children. As a mother of two children with autism said this fall in opposing restrictions on the ability of family members to provide consent for their children "If parents and legal guardians do not have the right to provide consent for people with autism [they] will be almost categorically deprived of the benefits that scientific research provides."

Failure to allow alternative procedures for providing consent would also compromise our efforts to produce new treatments for Alzheimer's disease and other illnesses. The National Institutes of Health have developed an innovative mechanism that allows fully functioning persons to designate someone else to make decisions for them when they are no longer able to choose whether or not to enter research projects. These and similar approaches have the greatest promise for protecting the autonomy and fulfilling the wishes of research subjects.

Studies Involving Medication Discontinuation and Symptom Challenge Studies

Questions have been raised about the appropriateness of studies in psychiatry and elsewhere in medicine involving discontinuation of medication and techniques that may result in exacerbation of patients' symptoms. Although it is not possible to address in detail here all of the complicated issues related to these types of studies, there are several important points that can be made.

First, such medication discontinuation studies have played and will continue to play a critical role in developing many new medications that can transform and save thousands of patients' lives. Patients' current medications may be discontinued as part of a research project for a number of reasons, including: to allow the old medication to leave the body so its effects are not confused with the effects of the new medication being tested, to permit study of the underlying

biological bases of a disorder without the distorting effects of medication, and in appropriate cases to test the utility of a new treatment against placebo.

Under these circumstances certain safeguards and protections for patients are essential. Needless to say, patients should be told clearly about the possible consequences of stopping medication and patients should participate only if they provide a competent informed consent. Provisions should be made for close monitoring of patients off medication, with clear criteria for reinstitution of treatment of significant symptom exacerbation occurs. And, of course, investigators should bear the burden in the first place of demonstrating why the advances of knowledge are significant enough to justify discontinuation of medication.

So called "challenge studies," in which attempts may be made to evoke some degree of symptomatology, are much less common. They may be used to elucidate the biological mechanisms responsible for a disorder, or to test possible new treatments. As with studies involving medication discontinuation, informed consent, careful monitoring, and a clear and important scientific rationale are essential. Moreover, both types of studies should exclude patients who are likely to suffer extreme distress or significant social, economic, or personal consequences if their symptoms reappear or worsen.

All research involves risk. Generally, we allow competent patients to decide to run these risks, after insuring that they have been well informed and appropriately protected, and that the study is likely to lead to knowledge proportionate to the risk involved. These same principles should apply to all medical research, including the classes of studies discussed here.

Conclusion

All of us must expand our efforts not only to prevent any lapses and abuses like those found at the West Los Angeles VA Healthcare Center from reoccurring but also to pledge ourselves to zero tolerance for these situations. APA believes, and we hope the members of this Committee will agree, that the pursuit of new knowledge and treatments for illness and the protection of the interests of research participants are not—and should not be seen as—mutually incompatible goals. I would like to thank you again for the opportunity to testify, and I look forward to continue working on these issues in greater detail with the Committee.

**The Unethical Use of Human Beings
in High Risk Research
Experiments***

Testimony
To

**Subcommittee on Oversight and Investigation
Committee on Veterans' Affairs
U.S. House of Representatives
United States Government**

By

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April 21st, 1999

¹The professional affiliation is given only for identification. I do not speak for the institution. I do speak for the organization, Citizens for Responsible Care and Research.

Dear Mr. Chairman:

I am Adil E. Shamoo from Columbia, Maryland (see Appendix for brief biography). I am here today to speak on behalf of thousands of vulnerable patients and their families not able or not willing to speak for themselves. I am here to speak on behalf of Citizens for Responsible Care and Research.

I would like to thank you Mr. Chairman and members of your Subcommittee for giving me this opportunity to inform you of my personal and my organization's grave concerns regarding the current ongoing research practices. Vulnerable human beings such as veterans with medical illnesses are being used as human subjects in high risk experiments with no medical benefits which cause them harm.

Mr. Chairman, a man serves his country; he comes back with a disability—post-traumatic stress disorder, or with depression or even schizophrenia. He turns to his VA hospital expecting the care and compassion. His doctor is the one who can help him the most. His doctor is his psychiatrist. He treats him and he becomes stable and functional. His doctor, however is also the researcher who conducts experiments on patients. His doctor asks him to sign informed consent. The doctor then proceeds to take him off medication abruptly. This causes him to become psychotic. In some instances he is left, in the community with psychosis, delusion, depression or post-traumatic stress disorder for weeks and months. Or, the researcher may administer chemicals such as cocaine or amphetamine or yohimbine (an African drug) to induce psychosis or delusion or post-traumatic stress disorder because he wants to study the illness. Is this fair?

Let me state at the outset that we support ethical research with human subjects where basic human rights are fully respected. But we do strongly oppose unethical research.

In March, 1996 (Shamoo, 1996) in a written testimony to the Committee on Governmental Affairs of the U.S. Senate, I stated: *"This type of research is on-going nationwide in medical centers and VA hospitals supported by tens of millions of dollars of taxpayers money. These experiments are high risk and are abusive, causing not only physical and psychic harm to the most vulnerable groups but also degrading our society's system of basic human values. Probably tens of thousands of patients are being subjected to such experiments."*

In 1994, we wrote to OPRR about unethical experiments at Bronx VA. It took OPRR five years to issue their report this January. In June, 1997 we wrote to NIH Director, Dr. Varmas, and in April, 1998 we also wrote to Secretary Donna Shalala about these unethical research experiments. Secretary Shalala did not reply and Dr. Varmas did nothing about it.

The recent revelations in The Boston Globe (Whitaker and Kong, 1998) and the LA Times (Monmaney, 1999) are only the tip of the iceberg about which the public learned. Evidence demonstrates the risk to patients who are veterans, or poor, or uneducated or elderly and seeking care in hospitals across the country. This is especially true if your illness is of a psychiatric nature such as depression, schizophrenia, and post-traumatic stress disorder to name a few. The recent suspension of VA hospital in Los Angeles by the Federal Office of Protection from Research Risk (OPRR) was in large part dealing with psychiatric patients (OPRR, 1999).

Decisionally impaired individuals should only be used as research subjects when it is in their best medical interest. Only under extreme, unique and rare circumstances should this population be ever used for research without direct medical benefit to them. And only when there is minimal risk involved.

The scope of the problem before us is truly unknown. There are 173 Veterans Hospitals across the country. All of these hospitals, their researchers, and their patients are intermingled with University's Medical Centers. There are probably hundreds of thousands of human subjects enrolled in research protocols across the country. I do not know nor I think it is possible to accurately know the exact number of veteran patients among them. My own survey of studies clearly indicates that veteran patients play a prominent role as human subject in the open literature.

The problems before us falls in one or more of the following categories:

1. Non-Compliance with the existing federal regulation.
2. Non-Enforcement of the existing federal regulation and
3. No independent oversight and no accountability
4. The need for legislative reforms of the federal regulation.

Allegations of abuse of patients with questionable decisional capacity include exposure to needless risks including, in some cases, suicides. These allegations have come to light from

families, patients, patient advocates, researchers surveying the published literature, conferences, media, hearings of the National Bioethics Commission and congressional hearings (NBAC, 1997). The recent decision by Dr. Steven Hyman, Director of the National Institute of Mental Health (NIMH), acting on the advice of a review panel, was to suspend 29 intramural clinical trials while requiring more than 50 additional studies —out of 108— to give adequate scientific justification for conducting them (Marshall, 1999).

The following are the four categories of problems with research that have come under scrutiny and criticism: (1) sudden medication washout studies. In these experiments, researchers take stable patients (many of whom are outpatients living at home), off medication and as a consequence, most relapse into psychotic states; (2) chemical provocation experiments (“challenge studies”) in which patients are injected with chemicals of no therapeutic benefit — such as cocaine, amphetamine, and ketamine (Special K), an animal tranquilizer in order to provoke severe psychotic episodes for the study of the “mechanism of psychosis.” (3) the fundamentals of informed consent are blatantly violated: patients incapable of comprehending the purpose of the research or the risks involved are asked to sign informed consent; insufficient information to make an informed decision; and duress and coercion are commonplace; and (4) hiding data on the number of suicides or attempted suicides of patients enrolled in psychiatric research, although, the incidence of suicide is very high in this population (for details on this topic see Shamoo and Irving, 1993, Shamoo and Keay, 1996, Shamoo et. al., 1997, Shamoo, 1997, Shamoo and O’sullivan, 1997, Lehman and Sharav, 1997) .

Examples of Unethical Research on Veterans

- (1) Behavioral vs. Biochemical Prediction of Clinical Stability Following Haloperidol Withdrawal in Schizophrenia. (van Kammen, 1995), a relapse experiment involved 88 veterans who had been stable and living in the community, when they were recruited and hospitalized for eight to ten weeks. Their medications were abruptly withdrawn and replaced by a standard dose of Haldol for 2 to 4 weeks, they were then “washed-out,” subjected to lumbar puncture, and observed for at least 6 weeks without medication to see who would relapse. According to the investigators, 50 of these patients had been subjects in their earlier studies – 30 had been used repeatedly in three separate experiments: (van Kammen, 1989; 1994; 1995) each involved lumbar punctures and abrupt withdrawal from all medications for six weeks to see who would relapse. In each experiment about

- 50% relapsed: it is not indicated how many times these 30 experimental repeaters relapsed.
- (2) Induction of Post-Traumatic Stress Disorder (PTSD) (Sowthick et al., 1997). 26 veterans were given a chemical called Yohimbine to induced PTSD.
 - (3) Induction of Post-Traumatic Stress Disorder (Brenner et al., 1997) on ten Vietnam Veterans with a chemical.
 - (4) In 1993, an experiment conducted at West Haven VA, on 12 inpatient and 15 healthy volunteers, a chemical called MCPP "*significantly increased*" the patients' psychotic symptoms, and they "*exhibited prolonged anxiogenic responses to MCPP.*" The authors indicate that: "*Schizophrenic are the only psychotic patient group studied to date.*"
 - (5) Between 1994-1997, we found four federally funded amphetamine experiments at New York VA Medical Center, (Wolkin, 1994; Sanfilipo, 1996); West Haven VA; (Laruelle, 1996); and NIMH (Breier, 1997). The investigators cite numerous previous studies in which stimulants were used in schizophrenia research, indicating that: "*Psychotic symptoms are exacerbated in approximately 40% of schizophrenic patients after doses of [central nervous system] stimulants....Moreover, a rather consistent body of data suggests that patients who show such symptom exacerbation are at increased risk for acute relapse if not taking neuroleptics.*" (Wolkin, 1994)
 - (6) In 1994, a double-blind experiment at NY VA Medical Center and Brookhaven National Laboratories, where two PET scans were conducted. Twenty-three schizophrenia inpatients were taken off their medications for a median period of 30 days; 17 were subjected to 0.5 mg/kg oral amphetamine challenge, and six served as placebo-controls. The investigators stated that the purpose of the study was "to specifically evaluate metabolic effects in subjects with varying degrees of amphetamine-induced psychotic exacerbation." (Wolkin et al., 1994)
 - (7) "Single Photon Emission Computerized Tomography Imaging of Amphetamine-Induced Dopamine Release in Drug-Free Schizophrenic Subjects" 1996. "The study was performed according to protocols approved by Yale School of Medicine and West Haven Veterans Affairs Internal Review Boards." The stated risks: "*Acute exposure to amphetamine induces emergence or worsening of positive symptoms in schizophrenic patients at doses that do not produce psychotic symptoms in healthy subjects.*" (Laruelle, p. 9236) Fifteen stable schizophrenia patients who were living in the community with "no current suicidal or homicidal ideation" (Lieberman et al., 1987) (emphasis added) were

withdrawn from their medications (for at least 21 days), then injected intravenously with amphetamine. They were then infused for over six hours with radioactive substance before having their brains scanned at West Haven VA Medical Center. The experiment induced the *"emergence or worsening of positive psychotic symptoms"* using *"a newly developed noninvasive method to measure amphetamine-induced dopamine release."* The report indicates, *"we could not assess the respective contribution of amphetamine and of the stress associated with the experimental setting to the indication of psychotic reactions."* (Laruelle et al., 1996)

The article claims patients included in this experiment *"were able to provide informed consent and to comply with this demanding protocol."* However, since the consent form signed by patient-subjects does not inform them about any risks associated with amphetamine, we wonder how they could do so. We also question how this consent form complies with federal requirements of full disclosure of the risks?

- (8) Repeated Amphetamine challenge to 13 patients (we are not certain they were veterans) (Strakowski et al., 1997). The patients were experiencing psychosis, delusion, hallucinations, or through disorder. However, the paper claims all provided "informed consent."
- (9) In 1994, we complained to the OPRR about an L-dopa experiment conducted on 28 veterans at Bronx VA medical center. These recovered veterans while living in the community were recruited into an experiment that was deliberately designed to induce psychotic relapse. All 28 veterans suffered the agony of psychotic relapse in order for the investigator to record how long it will take to relapse.

Testimonies of Patients and their Families

On September 18, 1997, patients and families testified before the National Bioethics Advisory Commission (NBAC, 1997) that they are victims of therapeutic neglect, betrayal of trust and institutional deception. The patients endured horrendous treatment in ill conceived, highly speculative, dangerous experiments which clearly undermined the best medical interest of the subjects, often causing them profound harm. These living witnesses represent countless others who have also been harmed and abused in experimental research but who remain silent. The families and patients testified that drug "washout" and placebo experiments were conducted without disclosure of known risks, in other words without informed consent: (1) Consent forms were often presented to subjects who could not understand them, and often presented after the

experiments were already under way. (2) Patient records were deliberately changed to fit the experimental protocol (3) Patients' medical and psychiatric conditions were allowed to deteriorate severely. (4) Patients were subjected to illegal use of restraints. (5) Patients were assaulted and injured by staff. (6) Experimental drug withdrawal procedures led to a suicide attempt. (7) One patient on a locked research ward was impregnated and then driven quickly to a clinic outside the institution to obtain an abortion.

High Risk and Unethical Research with Placebo Protocol

When medications are abruptly withdrawn in a research protocol, the relapse rate is as high as 80%. When is the risk to patients considered a sufficient deterrent to the researcher or to the Institutional Review Boards, which routinely approve such protocols? A schizophrenia relapse has serious, lasting, harmful consequences for the patient, it can even be life-threatening (Shamoo and Kewy, 1996, Shamoo et al, 1997).

Mr. Chairman, scientists know that in any study there are dropouts, people who suffer consequences of the study and quit. Thus, it is particularly disturbing that in 88% of the studies we looked at, the researcher failed to report any dropouts during research, and those that mention dropouts do not indicate the outcome or whereabouts of these human subjects.

Although the suicide rate among individuals with schizophrenia is very high, 1% per year, according to NIMH, we discovered that not a single suicide was reported in 41 US studies of thousands of patients over the past thirty years. This is in contrast to patients' and families recent testimonies that I just cited. This of course raises not only ethical concerns that patients have attempted or succeeded to commit suicide, which has never been reported, but it also raises the issue of the integrity of the research data reported. Attempted suicides are 8-25 times more than suicides. Were these suicides or attempted suicides ever reported to IRB's and other officials as required by the regulations? Why have FDA and OPRR not investigated unreported suicides and attempted suicides?

Ethics of High Risk Research on Decisionally Impaired

Three arguments have been used justify this type of research in the past: (1) subjects signed informed consent, (2) studies are not of high risk and thus reasonable, and (3) this was good for society, advancement of knowledge, and benefit for future generations. Most observers due to testimonies of patients and their families have discredited the first two arguments. Surveys

of past research practices and experiments of high risk have been shown to be harmful. The most cited argument that such research is good for society; is the utilitarian calculus that a few should suffer for the benefit of the majority. The proponent's claim that this research is acceptable if society's benefit exceeds the risk to the patients, (thus equating the interest of society with the interest of patient), and the claim that psychiatric patients have moral obligations to volunteer for research as subjects violate the Nuremberg Code and the Helsinki Declaration. Serving public good at the sacrifice of individual liberties, freedom, and autonomy Cannot be condoned except in the rarest circumstances such as the prevention of an epidemic by using quarantine, limiting individual liberties of citizens during their service in the army, conviction of crimes and other national emergencies. The advancement of drug development certainly does not fit one of these national emergencies. The fact is, the majority of mentally disabled individuals are not capable of giving truly informed consent.

We call for the following national reforms:

- I. **A moratorium on non-therapeutic, high risk experimentation such as abrupt drug "washouts" and "chemical provocation" experiments that are likely to exacerbate severe, incapacitating illness, and expose vulnerable persons to addictive drugs which may, with repeated exposure, lead to addiction and/or cause neurotoxic brain damage.**
- II. **Enactment of A National Human Subject Protection Act to provide safeguards for all human subjects in experimental research to provide regulatory safeguards for vulnerable human beings—at least equal to those currently provided to laboratory animals under the National Animal Welfare Act of 1966.**
- III. **A prohibition on conducting above minimal risk experiments on vulnerable persons who are incapable of evaluating the risks or appreciating the consequences to themselves—unless they can be demonstrated to be in their interest. An independent physician should assess mental capacity, and independent observers should monitor Informed Consent procedures.**
- IV. **Require that at least 51% of Institutional Review Board members be independent scientists and community representatives not affiliated with the institution. When considering the inclusion of vulnerable human subjects (e.g., children and mentally disabled persons) at least three additional voting members should represent the best interests of such vulnerable population.**
- V. **A comprehensive investigation by the Dept. of Justice or General Accounting Office (GAO) to determine the nature and scope of harm to subjects—including deterioration of**

their condition, relapses and suicide—caused by current and past practices in psychiatric research.

- VI. Adverse incidents to human subjects should be reported to the federal oversight board, indicating what preventive measures have been taken to prevent other such incidents. All physician-researchers should be required to report adverse incidents in drug trials to the FDA Physician Hotline – as physicians in clinical practice do or to OPRR.
- VI. Require a no-fault personal injury insurance for every human subject of research to cover the duration of the research and one-year following completion. We believe such insurance, in the amount of about \$250,000 per subject (premiums to be paid by the sponsor/research team/institutions) would be an incentive to reduce unnecessary risks and would compensate individuals/family for undue harm. It would also reduce the taxpayers' burden for uninsured persons who may require costly after-care as a result of experimental adverse consequences.

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Date: April 14, 1999

TO: Subcommittee on Oversight and Investigation
Committee on Veteran's Affairs
House of Representative

STATEMENT

I Adil E. Shamoo declare that I have not received any Federal grant or contract in the past two fiscal years.

Thank you.

Sincerely,



Adil E. Shamoo, Ph.D.
Professor

AES:ivr



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**Statement for the Record Submitted by the
 National Association of Veterans' Research and Education Foundations
 Regarding the Suspension of Research at the West Los Angeles VA Medical Center
 Before the Subcommittee on Oversight and Investigations and the
 Subcommittee on Health of the
 Committee on Veterans Affairs
 April 21, 1999**

The National Association of Veterans' Research and Education Foundations (NAVREF) appreciates the opportunity to submit a statement for the record to clarify issues regarding research-related reimbursement and cost sharing between VA medical centers and VA-affiliated nonprofit research corporations (NPCs). These are complex issues that we feel need more explanation than was provided during the April 21 joint hearing regarding the March 22 suspension of research at the West Los Angeles VA medical center.

1. Mandatory Reimbursement of the Medical Care Appropriation

As stated frequently by VA General Counsel, a guiding principle of the VA research program is that VA approved research is VA research. Consequently, upon approval by the local VA medical center R&D Committee, all research becomes VA research regardless of funding source—VA, university, corporation or other—and is subject to the same regulations, constraints, privileges, protections and support. VA appropriated funding for research is considered to be intramural funding; support from all other sources is considered to be extramural funding.

Regulations CFR 17.101(g) and M-1, Part I, Chapter 15.21 (Attachment A) specify mandatory reimbursement to the VA medical care appropriation for research related costs associated with patient care. Reimbursement is required only when medical services are provided to a veteran purely as part of an approved research project or to a patient who is not eligible for services as a veteran.

MP-4, Part V. 6C.08 a. (Attachment A) addresses VA administrative support services provided to medical research programs and states: *Costs of administrative support services to Medical Research programs will be borne entirely by the Medical Care appropriation.* "Administrative support services" include supply, building management, human resource management, fiscal services, etc. Section 6C.08 b. provides that the medical care appropriation will bear the entire cost of physician, dentist, and nursing services associated with research, unless otherwise approved by VA Headquarters.

2. Voluntary Cost Sharing

Research is both a cost and a benefit to VA. Last year, medical care appropriation support for research was estimated to be approximately \$310 million, the bulk of which was clinical staff time—physicians and nurses. However, there are many off-setting factors, including voluntary cost sharing by the NPCs. While an exact accounting is difficult, an analysis of a single diabetes clinical study administered by an NPC revealed a \$54,000 net gain to the VAMC in donated patient care services and drugs. Additionally, there are important intangible benefits from research such as improved care for veterans and an increased ability to recruit top quality physicians.

Regardless of the offsetting benefits, NAVREF has long recognized that VA medical centers cannot always support all the costs of extra- and intramurally-funded research. At many VA medical centers, the extramural research program is significantly larger than the intramural program and may strain research administrative support services that are tied to the size of the intramural, VA appropriated program. For example, Institutional Review Board (IRB) administrative costs are paid by the research appropriation; physician time spent serving on an IRB is paid by the medical care appropriation. This causes two problems:

1. If the extramurally funded program is as big or bigger than the intramurally funded program, administrative support dollars for the IRB pegged to the size of the intramural program may be inadequate to serve the entire research program at the facility.
2. Medical center management is understandably reluctant to use scarce medical care appropriation dollars to pay clinicians for time spent serving on an IRB instead of seeing patients.

To address the problem of how to provide necessary services in support of extramurally funded research, NAVREF encourages the NPCs to develop systems of voluntary cost sharing and many have done so. Consistent with VA General Counsel's affirmation that the NPCs are not prohibited sources under VA's gift authority, NPCs can and often do make research related in-kind and cash "gifts" to VA medical centers including:

- Donating IRB administrative staff, clinical nurses, pharmacists, custodians and animal facility workers.
- Purchasing and donating furniture, office and research equipment, and supplies.
- Providing seed money so investigators can develop new grant proposals as well as bridge funding to maintain laboratories between projects.
- Setting up an endowment to ensure that there will be permanent stream of funding to be spent at the discretion of the board of directors and VA research service administrators.
- Supporting the costs of recruiting clinicians with a research interest.
- Paying all or part of a VA medical center's hazardous waste disposal costs and other bills that increase as a result of NPC-funded research.
- Helping pay the cost of upgrading outdated or creating new research space.

The list could go on and on. However, the point is that despite some constraints, the NPCs can and generally do make substantial contributions to the research program, and, indirectly, to clinical services at the affiliated VA medical center.

Clarification of Issues Raised in Testimony During the April 21 Hearing

1. The VERA research allocation is a well-intentioned effort to recognize that research support has an impact on the medical care appropriation. Unfortunately, this is an imperfect and largely ineffectual means of addressing the problem because 1) there is no accountability requiring that the research allocation be returned to the facility that earned it or that it be spent on medical care services in support of research (largely staff time) and 2) the VERA allocation is simply recycled medical care money rather than "new" money.
2. A VA medical center may not charge an NPC for services the medical center is obligated to support (by statute or regulation) unless a VA-approved contracting mechanism is used to reach a mutually acceptable agreement providing that the corporation will pay for certain services.
3. When reimbursement of the medical care appropriation is required, such reimbursement must be provided to the medical care appropriation. It may not be directed to the research appropriation.
4. NPCs can and do provide research related in-kind and cash contributions to VA medical centers. For example, in 1998, the board of directors of the Brentwood Biomedical Research Institute (BBRI), the NPC affiliated with the West Los Angeles VA medical center, approved cash donations to the medical center in support of the VA research program. One was for \$225,000 comprising a cash donation plus a write-off of debt the VA research program owed BBRI for staff provided to VA under the Intergovernmental Personnel Act. The second, in late 1998, was a cash gift of \$204,000. Also in late 1998, the BBRI board committed approximately \$180,000 to hire and donate BBRI staff to the VA research service to support IRB services through the remainder of the 1999 federal fiscal year.

Conclusion and Recommendations

NAVREF has long been aware of problems related to medical care support for the VA research program. These problems are being exacerbated as the VA-funded portion of the program shrinks as a percentage of the total VA research enterprise. NAVREF does not recommend any change in the guiding principal—VA-approved research is VA research. Rather, NAVREF recommends that VA engage in equitable cost sharing of the research sponsored by all of its research partners. Of course, off-setting contributions should be factored into any such cost sharing determinations.

NAVREF regularly encourages the NPCs and VA to pursue cost sharing opportunities. For example:

1. More NPCs now charge pharmaceutical companies a fee for IRB review and use the resulting funds to hire and donate IRB support staff.

2. NAVREF supports those NPCs that administer NIH grants on behalf of VA investigators, often despite objections from affiliated universities. Such NPCs tend to use the amounts that accrue from the associated NIH indirect costs to benefit VA to a greater degree than affiliated universities. Last year, one such NPC paid nearly \$1 million in reimbursements to VA and direct payment of bills incurred to support NIH-sponsored research administered by the NPC and conducted in the VA facility. If those same NIH grants had been administered by the affiliated university, it is likely that the VA medical center would have absorbed those costs.
3. Finally, NAVREF is working with universities to persuade the Department of Health and Human Services and the National Institutes for Health to implement new policy that would provide a 15% "VA-add on" indirect cost rate for all NIH-sponsored research conducted in VA facilities, but administered by affiliated universities (see Attachment B for details).

As OPRR representatives stated during the April 21 hearing, most IRBs are underfunded and understaffed. Because it is an intramurally funded program supporting a great deal of extramurally funded research, VA seems particularly impacted. To address problems of oversight and the need for additional resources, NAVREF strongly supports the new oversight initiatives VA is implementing and encourages VA to be creative in identifying and pursuing new, non-VA resources to address chronic shortfalls. However, a robust research appropriation is essential to assure that VA can sustain its current level of research activity and at the same time implement oversight programs that will set a new national standard.

Thank you for considering our views.

Comments or questions regarding this statement may be addressed to NAVREF Executive Director Barbara West.

CFR 17.101 Charges for care or services.

(g) Furnished for research purposes. Charges will not be made for medical services, including transportation, furnished as part of an approved Department of Veterans Affairs research project, except that if the services are furnished to a person who is not eligible for the services as a veteran, the medical care appropriation shall be reimbursed from the research appropriation at the same rates used for billings under paragraph (b) of this section.

M-1, Part I, Chapter 15. 21

- a. When medical services are furnished on an inpatient or outpatient basis as part of an approved research project to a person (veteran or non-veteran) purely for the research program and not as a part of approved medical care to an eligible veteran, the research appropriation must reimburse the medical care appropriation according to provisions of VA Regulation 6062 (G) at the applicable rates in accordance with Appendix 15A. Billing for services obtained from non-VA sources exclusively for research purposes (travel, special procedures, etc.) will be for the same amount charged the VA.

MP-4, Part V. 6C.08

- a. Costs of administrative support services to Medical Research programs will be borne entirely by the Medical Care appropriation. These services include support activities such as fiscal, supply, building management (400 and 500 series of accounts), etc.
- b. Other costs to be borne entirely by the Medical Care appropriation are those for services of physicians, dentists, and nurses engaged in research work on less than a full-time basis and for whom placement on Medical Research roles has not been specifically approved by Central Office.

VA and University Stakeholders' Support Needed to Promote 15% "VA-Add On"

The Department of Health and Human Services (HHS) and the National Institutes of Health (NIH) have indicated a willingness to consider applying a 15% "VA-add on" to the negotiated indirect cost rate for NIH grants administered by affiliated universities on behalf of VA investigators. The 15% would be "added" to the administrative off campus rate—usually 26%—received by the university. This plan can be considered a win-win model with universities maintaining their normal reimbursement for administrative costs and the VA receiving reimbursement for the infrastructure costs of supporting NIH-sponsored research in their facilities. To persuade NIH and HHS to move this concept toward implementation, HHS/NIH need to hear from VA and university stakeholders.

Background: In recent years, some VA-affiliated nonprofit research corporations (NPCs) have obtained HHS-approved indirect cost rates—now referred to as Facilities and Administration (F&A) rates—and are administering NIH grants for VA researchers (San Francisco and San Diego among others). Historically, however—and more commonly—VA-affiliated universities administer NIH grants on behalf of VA investigators. For grants conducted primarily in VA facilities, NIH provides the recipient university with its HHS negotiated off-campus indirect cost rate for the administration component of the university's costs.

Current HHS policy does not allow reimbursement of indirect costs on grants to federal agencies. This has been interpreted to preclude NIH from reimbursing VA hospitals for costs incurred in support of NIH-sponsored research. As a result, VA medical centers typically support the indirect costs associated with NIH research conducted in VA facilities. These costs may include custodial services, waste disposal, building repair and maintenance, safety training/monitoring, library, telephone and various support services such as warehouse, mail, and WOC processing, etc., that increase incrementally as a result of NIH-sponsored research conducted in VA facilities.

VA Add-On: To address this imbalance, NAVREF recommends a new HHS policy that would add 15% to a university's off campus F&A rate to be used to reimburse VA medical centers for their incremental costs. This would be applicable only in instances where local choice and circumstances dictate that the university (rather than the VA-affiliated corporation) act as the grant recipient, and the majority of the work is conducted in a VA facility.

- **Various VAMCs that have applied to HHS for a VA-add on (White River Junction, Seattle, West Haven) have provided sufficient justification for reimbursement ranging from 14.5% to 16%.** Based on these detailed analyses, a flat national rate of 15% is recommended. Notably, a 15% overhead rate is routinely provided on NIH/VA interagency agreements (these are contracts, not grants so HHS rules do not preclude reimbursement). This establishes precedents for 1) the 15% rate; 2) the notion that VA medical centers can receive and retain locally reimbursement for indirect costs on NIH-sponsored research; and 3) recognition that the sponsoring agency should support the direct and indirect costs of its own research.
- **The VA add-on would strengthen the university-NIH-VA partnership.** Universities still would receive and retain their off-campus rate. By supporting the costs of its own research, NIH would benefit from VA's increased ability to support research. And VA would be in a better position to support NIH-sponsored research as a result of having available new money to relieve some of the pressure research imposes on the medical care appropriation.

- During 1998, the VA-add on would have generated as much as \$30 million for VA medical centers to cover costs that currently are being supported by VA's medical care appropriation. Last year, VA investigators received NIH awards totaling \$267 million. Recognizing that some grants qualified for the university's on-campus F&A rate and would have been excluded from the VA add on, \$30 million is a "best guess" estimate of the potential cash flow. When VA provides NIH with the necessary data, NIH is willing to conduct a detailed analysis to arrive at a more exact figure.
- Under the VA-add on, funds would flow from NIH to universities to VA medical centers. To avoid burdening these funds with constraints imposed on VA-appropriated dollars, it is likely that VAMCs would designate their affiliated NPC as the entity that would administer the funds on behalf of the VAMC. This is allowable under current HHS policy. It is also anticipated that VAMCs and NPCs would have to demonstrate that the funds are expended in ways consistent with HHS regulations (i.e., for research support), just as NIH requires accountability on F&A expenditures from universities.

Action Needed:

- VA stakeholders must request that HHS/NIH approve the VA-add on. Although NAVREF and various medical centers have been pursuing the VA-add on concept for several years, VA stakeholders have not yet voiced their interest directly to HHS/NIH policymakers. Understandably, NIH management is not going to argue in favor of paying more F&A on grants until VA stakeholders make their case and VA cooperates in resolving the pertinent policy and logistical issues. We strongly encourage VA stakeholders to be proactive in pursuing the VA-add on.
- University stakeholders must communicate to HHS/NIH their support for the VA-add on. Recognizing that every dollar spent on F&A means a dollar less for grants, the VA add-on may face political resistance at the top levels of HHS and NIH management. However, during a meeting on February 4, senior HHS and NIH personnel indicated a willingness to advance this concept if a sufficient number of their traditional partners—particularly academic medical institutions—support the VA-add on as both appropriate and necessary to foster the university/VA/NIH partnership.

Stanford University has already sent a letter of support (Attachment 1). The following institutions have indicated that they will send letters shortly:

- | | |
|--|---|
| ▪ Univ. of Washington School of Medicine | ▪ University of California, Los Angeles |
| ▪ Dartmouth Medical School | ▪ School of Medicine |
| ▪ Yale University School of Medicine | ▪ University of Florida College of Medicine |
| ▪ University of Texas SW Medical School
(San Antonio) | ▪ University of Minnesota Medical School |

While these are a start, far more letters are needed. We strongly encourage VA senior management to urge their academic affiliates to send HHS/NIH letters of support. Letters should be addressed as follows:

Ms. Diana Jaeger, Acting Director
Office of Policy for Extramural
Research Administration (OPERA)
National Institute of Health (NIH)
6701 Rockledge Drive, MSC 7730
Bethesda, MD 20892-7730

Mr. Joe Cook, Director
Office of Audit Resolution and Cost Policy
Department of Health and Human Services (DHHS)
200 Independence Ave. SW 522E
Washington DC 20201

A sample letter is provided as Attachment 2. Please send a copy of your affiliated university's letter to NAVREF so we may compile a complete list of supportive institutions.

Questions or comments regarding the VA-add on may be directed to NAVREF Executive Director Barbara West. Phone: 301-229-1048. Fax: 301-229-0442. Email: navref@navref.org. Thank you for your interest.



STANFORD UNIVERSITY
Office of the Associate Vice President for Research Administration

March 18, 1999

Ms. Diana Jaeger
National Institutes of Health
6701 Rockledge Drive
Suite 2188
Bethesda, MD 20892-7730

Dear Diana:

I understand that you had a meeting this past month with staff from the Department of Health and Human Services and the Veterans Administration (VA) regarding reimbursement for facility and administrative costs (F&A) on grants for activities taking place in VA facilities. I thought it might be helpful to provide some background on Stanford's interest in this particular matter. First of all, we want to continue to have Stanford University faculty who hold dual University/VA appointments and whose laboratories are located at our affiliated VA facility to apply for grants through the University. The opportunity to create or engage in cutting edge research is a main attraction for academicians at the Stanford University School of Medicine and the VA Palo Alto Health Care System is an integral component in this program. Further, the VA patient population is an important group for many clinical trials conducted by our faculty and, therefore, an important resource to NIH as well.

The principal reason that we are interested in having Stanford University continue to be the grantee institution is a programmatic one. We wish to ensure that all the faculty, regardless of where they have their clinical appointment or where they work, have access to equal support for their research activities. We want the faculty to pursue their research through the Medical School so the Dean and the Department Chairs have an understanding of and oversight over all of the research activity of the faculty, not just part of it. Further, by retaining administrative responsibility for these grants, we assure that a single standard is applied in the administration that supports this research, the protection for human subjects, and the humane care of animals. We want to minimize the perception that resources for those investigators and laboratories located on campus are different than or richer than those that are off campus.

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Ms. Diana Jaeger
March 18, 1999
Page 2

When there is no support for VA facilities' costs, this becomes a real challenge. The VA is supporting the incremental facility costs associated with NIH supported grants of Stanford faculty working at the VA. And, clearly there are incremental costs associated with the conduct of research above and beyond the cost of clinical care in these facilities such as utilities, operations and maintenance, biosafety, etc. The costs are no different in that respect than if they were occurring in Stanford-owned facilities. As VA budgets shrink, so does the willingness and ability of VA administrators to continue to bear this burden. So, of course, we believe that in order to be equitable NIH should reimburse these facility and administrative costs on the same basis, without distinction for the fact that they are VA facilities.

I know that one of the stumbling blocks has been whether the VA is authorized to receive reimbursement for these incremental facility costs. I have been assured by colleagues here that they can. I presume that the VA staff in Washington can confirm that on behalf of all VA Hospitals.

So, we approach this issue with an interest in receiving a reasonable reimbursement to the VA for the incremental costs of research in their facilities through the Stanford F&A rate. We are developing an off-campus VA specific rate for those costs that we think are eligible for reimbursement. While we are interested in a university-based F&A rate of reimbursement, it probably would be comparable for those who are seeking to reimburse the VA for research conducted through their affiliated foundations. We might even be willing to entertain an "allowance" or a flat rate for the facility portion of the costs, e.g. 15 percent. We would add such an allowance to our off-campus rate for administrative and library expenses for the total reimbursement.

I hope that this background helps in future discussions you may have on this issue. We will proceed with some exploratory discussions with the Office of Naval Research for inclusion of an off-campus VA specific rate for Stanford. In the meantime, note how fitting it is that I write to you on this subject on March 17! If I can provide any further information, please let me know.

Sincerely,



Geoffrey E. Grant
Associate Vice President for Research Administration

GEG:lr
F:GG2/99

Sample University Letter In Support of VA-Add On
Please paraphrase and add locally relevant examples and details.

Date

Address separate letters to:

Ms. Diana Jaeger
 Acting Director, Office of Policy for
 Extramural Research Administration
 (OPERA)
 National Institute of Health (NIH)
 6701 Rockledge Drive, MSC 7730
 Bethesda, MD 20892-7730

Mr. Joe Cook
 Director
 Office of Audit Resolution and Cost Policy
 Department of Health and Human Services
 (DHHS)
 200 Independence Ave. SW 522E
 Washington DC 20201

Dear :

I am writing to indicate my support for appropriate sharing of the indirect costs associated with National Institutes of Health (NIH)-sponsored research conducted in Department of Veterans Affairs (VA) facilities. I strongly support the concept of a "VA add on" facilities and administration (F&A) rate over and above our usual indirect cost rate when studies are administered by the (university name) and the work is conducted at our affiliated VA (VAMC name).

Provide specific local examples of the cost benefit to your university and NIH of conducting university-administered, NIH-sponsored research in partnership with your VA. See attached Stanford letter. Other possible benefits: faculty access to VA laboratory and clinical space often negates the need for additional university construction at NIH expense; shared equipment reduces overhead; and even with the VA-add on, total F&A may be lower than the university on-campus rate. Please detail similar mutually beneficial arrangements with your affiliated VA that impact NIH costs or foster research collaboration with your VA.

I encourage the Department of Health and Human Services (HHS) and NIH to finalize policy that will allow equitable sharing of VA's costs in support of NIH research. The concept of a "VA add on" indirect cost rate of 15% added to our off campus F&A rate seems to me a reasonable mechanism to share costs. The 15% rate appears to be both justifiable and of sufficient size to have positive effect on our VA's ability to provide the support necessary for NIH research conducted in its facilities. The (name of university) currently administers (number of NIH grants) grants on behalf of faculty with joint VA/university appointments. We would view very positively a change in policy that would allow VA to recoup some of the costs it is incurring in support of these grants.

Our longstanding, highly productive partnership with the (name of VAMC) is extremely important to both institutions. A mechanism such as the proposed VA-add on would foster and strengthen this relationship. I strongly encourage HHS and NIH to act expeditiously to implement policy that would provide rational mechanisms for NIH to assume responsibility for a reasonable share of the costs incurred by NIH-sponsored research conducted in VA facilities. Thank you for considering my views.

Sincerely,

University President or Designated Signatory

Cc: VAMC Medical Center Director
 ACOS R&D

**Pre-Hearing Questions
Concerning the April 21, 1999, Hearing**

**for
The Honorable Kenneth W. Kizer, M.D., M.P.H.
Under Secretary for Health
Department of Veterans Affairs**

**from
House Committee on Veterans' Affairs**

**Representative Terry Everett
Chairman
Subcommittee on Oversight and Investigations**

**Representative Corrine Brown
Ranking Democratic Member
Subcommittee on Oversight and Investigations**

**Representative Cliff Stearns
Chairman
Subcommittee on Health**

1. The immediate steps being taken, including outreach, to ensure that patients in the West Los Angeles and Sepulveda research programs receive essential medications that were part of the research protocols.

Answer:

Upon notification of the impending suspension of research activities by the Office for Protection from Research Risks (OPRR), Department of Health and Human Service (HHS) and Veterans Health Administration (VHA) Headquarters, the VA Greater Los Angeles Healthcare System (GLAHS) reviewed all protocols underway to identify those that, if discontinued, might cause risk or harm to the health and safety of human or animal subjects. The investigators themselves undertook a first level review, since they were the most knowledgeable about the projects. Other clinicians and administrators with knowledge about the projects also conducted reviews to assure that studies with potential human or animal risk were not overlooked.

If there was any question as to potential risk to human or animal subjects, the research was authorized to continue in a "maintenance" mode. That is, all medications, treatments and interventions were allowed to continue with existing subjects, but no new enrollees were permitted.

GLAHS developed an informational memorandum to distribute to investigators informing them of their responsibility to reach out to patients in their studies, provide them with information about the research suspension and assure them that they would not be in any danger and that their medications and treatments would continue. "Talking points" were developed and distributed to assist investigators in speaking with their subjects. Likewise, investigators were repeatedly reminded at town hall meetings of their responsibilities to contact their patients. These communications were also made available to public affairs officials, patient representatives, veterans service organizations, contacts at the university affiliates, and administrative officials. I am advised that they also have been posted on GLAHS and Veterans Integrated Service Network 22 inter- and intranet pages.

In addition, GLAHS management reports that it held several discussions specifically with the research pharmacist and a memorandum was developed to her emphasizing that all study medications were to continue to be dispensed for continuing projects. This information was shared with other members of the GLAHS pharmacy staff as well.

2. The specific problems with human, animal and basic medical research at West Los Angeles and Sepulveda.

Answer:

VHA considers the protection of human and animal subjects and our laboratory employees to be among our highest priorities. Dating to a site visit in September 1996, VHA Headquarters has had concerns about the administration of the Research Service at the West Los Angeles campus, in particular. Additionally, in spring 1997, the National Institute on Drug Abuse (NIDA) raised concerns about the financial management of a VA-NIDA collaborative agreement for medication development by the Research Service at the West Los Angeles facility. In May 1997, the Chief Research and Development Officer (CRADO) placed the West Los Angeles Research Service on administrative probation. This history of financial management concerns, coupled with new and historical concerns about administration of human, animal, and bio-safety research (described below), led VHA to suspend all research conducted at GLAHS as of March 26, 1999.

Human Studies

On March 22, 1999, OPRR deactivated its Multiple Project Assurance (MPA-1087) for GLAHS, which encompasses the former VA medical centers at West Los Angeles and Sepulveda, and affiliated clinics. MPA-1087 is the mechanism by which GLAHS assures OPRR that GLAHS conducts its research involving human subjects in conformance with 45 CFR 46. This HHS regulation incorporates 52 FR 28003, also referred to as the "Common Rule" for the protection of human subjects in research and which is subscribed to by 17 federal agencies that fund research involving human subjects.

As permitted under the Common Rule, VA accepted MPA-1087 as its own assurance that VA research at GLAHS was conducted in accordance with federal regulations. Moreover, since VA considers all research, regardless of sponsor, conducted at VA medical centers to be VA research, MPA-1087 covered all human research conducted at GLAHS whether HHS, VA, or any other source funded it. Consequently, OPRR's actions effectively removed all assurance that research involving humans being conducted at GLAHS was in legal and ethical compliance.

OPRR's deactivation of MPA-1087 resulted from the failure of GLAHS to adequately respond since April 1993 to requests by OPRR to change and/or document procedural and administrative matters related to the way GLAHS conducted initial and ongoing reviews of protocols involving humans. Specific problems cited by OPRR included:

- meetings of Institutional Review Boards (IRBs) – these committees are responsible for the review and monitoring of human studies protocols – that did not meet with a quorum of voting members as required by 45 CFR 46;
- the absence from IRB membership roles of appropriate community/patient representatives;
- Data Safety Monitoring Boards had not been established by GLAHS as requested by OPRR in 1994;
- inadequate procedures for continuing review of ongoing projects;
- failure to implement policy changes recommended by OPRR; and
- the use of "expedited review" procedures by IRBs to approve research studies with greater than minimal risk in contradiction to the requirements of 45 CFR 46.

Most of these infractions occurred at the West Los Angeles campus of GLAHS. Since the merger of West Los Angeles and Sepulveda, both campuses have operated under the same MPA. Thus, the deactivation of the MPA-1087 affected both campuses, even though the concerns focussed on West Los Angeles.

Animal Studies

Both the West Los Angeles and Sepulveda campuses have problems with their animal programs, but those at Sepulveda are more serious.

A report of the Institutional Animal Care and Use Committee (IACUC) of the GLAHS Research and Development (R&D) Committee found that the laboratory animal care facilities at the West Los Angeles campus were acceptable. A site visit by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) to the West Los Angeles animal care facility found that the occupational risk of animal handlers had not been assessed properly and is now requiring changes in policies and procedures. AAALAC's final report on West Los Angeles is pending. It is likely AAALAC will recommend additional minor policy and procedures changes and place the West Los Angeles campus under restriction until it is satisfied that the problems have been rectified. Additionally, in April 1998, the Medical Research Service, Office of Research and Development (ORD), VHA Headquarters, expressed its concern to the Associate Chief of Staff for Research (ACOS-R) at the West Los Angeles facility about the lack of progress to correct infrastructure and leasing deficiencies related to building 337 and about attempts to pressure members of the Institutional Animal Care and Use Committee (IACUC) inspection report. Although requesting a response within seven working days, none has been received.

At the Sepulveda campus it is anticipated that AAALAC will place the animal facility on probation for multiple program deficiencies related to the occupational risks of animal handlers and specific problems with animal housing, such as temperature, humidity and crowding.

Non-Human/Non-Animal Studies

This classification covers virtually all basic research. The VHA Headquarters Emergency Management Site Visit Team that visited GLAHS on March 25-26, 1999, found serious deficiencies in the bio-safety program at GLAHS, in particular at the West Los Angeles campus.

- Required reviews of research protocols for bio-safety issues were done by a junior investigator without appropriate expertise for all hazards being reviewed.
- No minutes of the Bio-Safety Subcommittee (a subcommittee of the R&D Committee) documented any kind of bio-safety review. The reviews existed only in draft form in the reviewer's laptop computer.
- The Bio-Safety Subcommittee accepted verbal reports from the reviewer without written documentation of review.
- Bio-Safety Subcommittee minutes are more than six months in arrears—i.e., over six months of minutes are missing. R&D Committee minutes repeatedly note that Bio-Safety Subcommittee minutes are missing, but no action had been taken to correct this problem. Since the R&D Committee is supposed to accept committee reports as final approval, none of the bio-safety studies has had proper approval for months.

The Emergency Management Site Visit Team found no significant problems at the Sepulveda campus with respect to bio-safety issues.

3. The recovery plan and timetable for the West Los Angeles and Sepulveda human, animal and basic medical research programs to resume operation, including prioritization of the projects.

Answer:

A full Recovery Plan for research at GLAHS has been developed. The following is a brief summary of that plan. A copy has previously been provided. The Recovery Plan has seven phases, each with a number of specific actions anticipated.

Phase 1

- The GLAHS is notified on March 22, 1999 that all research activities will be suspended on March 26, 1999.

- Research suspended encompasses all human, animal, non-human/non-animal research at the West Los Angeles, LA Outpatient Clinics, and Sepulveda campuses of GLAHS. Exceptions are made for human and animal studies whose suspension could place research subjects at risk if respective studies were stopped abruptly.

Phase 2

- Total research suspension in effect and all VA research funds are withdrawn on March 26, 1999.
- On-site Emergency Management Team from VA Headquarters is on-site at West Los Angeles and Sepulveda on March 25-26, 1999.

Phase 3

- Full-scale site visit team at GLAHS to assess status of entire research program April 5-9, 1999.

Phase 4

- Partial research suspension in place (expected April 1999 after review of site visit report); external management team in place (ACOS-R and Administrative Officer detailed from other facilities). If the site visit team identifies specific components of the research program that are functioning properly, legally, and ethically, it may recommend to the Under Secretary for Health that discrete components of the research program should be re-instituted.

Phase 5

- Research suspension removed partially, but probation in place (expected action in April-May 1999); interim management team (internal leadership) identified;
- Re-constitution of the research administrative and oversight functions completed;
- Probationary period and HQ monitoring instituted.

Phase 6

- Suspension removed, probationary period in place (1999); expected minimum duration May 1999-May 2000;
- National search for new, permanent ACOS-R.

Phase 7

- Probationary period in place to extend one year after appointment of the new, permanent ACOS-R (likely May 2000-May 2001).

4. The researchers, management and program officials responsible and held accountable for the deficiencies that led to the suspension of research.

Answer:

When GLAHS and VISN 22 were informed of the research suspension, the Acting ACOS-R for GLAHS, Dr. Steven Pandol and the Acting Administrative Officer for R&D, Ms. Marnell Davis, were detailed to other administrative and clinical assignments, as appropriate. An inquiry into all research-related issues has been launched by VISN 22 and VHA Headquarters. Preliminary findings from various components of the investigation make it clear that these individuals cannot return to their prior positions. Any formal, final actions will result from, and be consistent with, the findings and recommendations of the investigations. The Chairs of all key research-related committees have been replaced, including the Chairs of the R&D Committee, the Biosafety Subcommittee, and the Chairs of all Institutional Review Boards/Human Studies Subcommittees.

5. The reasons why the matters involving Dr. Bramah Singh and Dr. Philip Sager were not properly reported to VA Central Office and the Department of Health Human Services Office for Protection from Research Risks, and who was responsible for reporting them.

Answer:

It appears that there were several factors that contributed to the lack of formal reporting of the February 1996 Board of Investigation involving Drs. Sager, Gallick and Singh to VHA Headquarters. The investigation was conducted as an official Board of Investigation to address a clinical matter, as opposed to being conducted under established departmental policy, "Misconduct In Scientific Research" (M-3, Part I, Chapter 15), under which violation of human subjects research protections are covered. This policy clearly delineates a reporting requirement to VHA Headquarters, whereas Boards of Investigation generally do not.

GLAHS officials have indicated that they were unaware of the scientific misconduct policy and procedures and were not at any point advised to conduct their investigation under that policy. At the time of the Board of Investigation, a number of VA officials and offices were involved to varying degrees, including the Office of Clinical Affairs and local Research and Development and Human Resources staff. Apparently, none of these individuals or offices advised a course of action other than that which was pursued under the Board of Investigation. VHA will ensure proper education at GLAHS regarding these requirements in the future and will similarly convey that all Networks and facilities should be cognizant of the requirements concerning investigations into research issues. VHA's ORD also will conduct a systemwide training program – e.g., a satellite/video teleconference – on lessons identified from the GLAHS experience.

When VHA HQ ORD became aware of the matters cited here, it forwarded the material to OPRR in March 1999. Because VA recently determined that the research apparently did not involve HHS funding, it turns out that OPRR would not have had jurisdiction over the case. Nevertheless, had the initial Sager investigation been conducted as a research misconduct matter, notification to OPRR would have been judged as appropriate, or not, in a contemporaneous fashion. Clearly, the appropriate bias – then and now – should be in the direction of VA reporting to OPRR.

6. The extent to which VA legal counsel was involved in the settlement executed May 8 and 9, 1996, with Dr. Sager, the authority of the hospital Chief of Staff to enter into such an agreement, whether the Chief of Staff had a conflict of interest because he had a motive to conceal or minimize problems in the research programs, and whether the chair of the board of investigation on Dr. Sager had a conflict of interest because she was a co-researcher on a project with him.

Answer:

The referenced "Settlement Agreement" with Dr. Philip Sager was, in fact, a "Memorandum of Agreement" that resulted from Dr. Sager's admission of misconduct and willingness to waive his rights at the time to all due process. Management officials at the then West Los Angeles VAMC, in consideration of the existing dysfunction in the Cardiology Department, report that they considered it advantageous to avoid a protracted and potentially litigious experience with Dr. Sager. Legal Counsel was not involved in the Memorandum of Agreement dated 5/8-9/96, entitled "Alternative to Discipline," since the facility posits there was no requirement that they be so involved.

The Chief of Staff, Dr. Dean Norman, was operating under authority delegated to him by the Medical Center Director. He was the accountable official for clinical operations, the President of the Medical Staff, and the accountable official to whom both the then ACOS-R, Dr. Steven Pandol, and the Chief of Medical Service, Dr. Phyllis Guze, reported.

The facts as follow belie the notion that the Chief of Staff had a motive to conceal or minimize problems in the research program:

- Dr. Norman supported Dr. Guze's request of UCLA Emeritus Dean Sherman Mellinkoff that he intervene, assess and report on problems in the Cardiology Department
- When notified of problems in the Department that were unresolved and inadequately addressed, despite Emeritus Dean Mellinkoff's efforts (and those of

Drs. Berson, Singh, Guze and Haskell), Dr. Norman directed that the Board of Investigation be convened.

- The chair of the Board of Investigation was Dr. Thomas Gerrick, a noted psychiatrist of eminent standing among his VA and UCLA colleagues, and an experienced chair of VA Boards of Investigation. He had no professional alliances with any of the Cardiology Staff who were the subjects of the investigation.
- Dr. Pamela Steele did not chair the Board of Investigation. Some years ago she had been listed as a co-author on an abstract with Dr. Sager that was published after the Board of Investigation was complete. The abstract addressed VA data related to Automatic Implantable Cardioverter-Defibrillators and was written by Dr. Ross Fletcher at the Washington, DC VAMC. Dr. Steele appeared on that abstract as a member of the research group at Washington, DC VAMC, which had participated in data collection. Dr. Sager was identified because of his contribution to the data set based on his role elsewhere. The record of the Board's conduct and conclusions to address the issues it was charged to investigate stand as testimony that her service apparently did not influence the outcome. In retrospect, VA acknowledges that it is inadvisable to convene Boards of Investigations involving individuals where there might be even a *perception* of a potential conflict. Network and facility officials will be directed to take steps to avoid this in future Boards.

7. Whether performing medical research on veteran patients without informed consent constitutes patient abuse, and whether VA has investigated or reported any criminal behavior in connection with failures to obtain consent from veteran patients for medical research on them.

Answer:

In general, performing research on veteran patients without informed consent may constitute a battery and might constitute "patient abuse" depending upon the circumstances and facts of each case.

I am advised that on one occasion, the Acting Chief of Staff, GLAHS, Dr. Dean Norman, consulted by telephone with the Regional Counsel in Los Angeles. Based on the facts presented to the Regional Counsel, he found no support for a finding of criminal activity.

8. Whether VA has reported any individuals to state or other licensing authorities in connection with any of these matters.

Answer:

Not as of this date, but the matter is presently under review. It should be noted that, until late 1996, VA could not by regulation directly report any current employees to state or other licensing authorities – only those separated from service. The facility could have restricted the clinical privileges for an individual (or individuals) for 30 days or more, and this would have been reportable to the National Practitioner Data Bank (NPDB). NPDB is not a licensing authority, but when reports are made to it, state licensing boards receive the information and might launch their own queries.

9. The steps being taken to determine whether these or similar problems exist elsewhere and whether other failures to properly report incidents have occurred.

Answer:

A broad series of initiatives to assess the systemic nature, or lack thereof, have been underway for some time:

- In 1995, the VHA Office of Standards in Human Research was formed and located at the Portland VAMC. Since its inception, the office has conducted 12 random site visits to medical centers across the country. Site visit teams reviewed: IRB records, informed consent documents, all local policies and procedures in place to implement national requirements under the Common

Rule, FDA regulations, and VA manual M3, Pt.1, Ch.9. In addition, medical center directors, chiefs of staff, associate chiefs of staff for research, and researchers were interviewed. At the sites visited, the site visit teams found failures in documentation, but no instance of violation of any patient's rights or health and well-being, and no instance of either willful or intentional misconduct.

- The VHA Cooperative Studies Program Human Studies Committees conduct 12 performance sites visits per year. Along with audit activities, the committees also interview research volunteers regarding their experience as a research participant, including an assessment of the subjects' informed consent.
- The VA Cooperative Studies Program on average conducts 45 audits per year of its drug studies at selected performance sites.
- The VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center is FDA-approved for packaging, dispensing, and monitoring pharmaceuticals and devices for drug trials. The Coordinating Center audits each trial at each study site at least once during the life of the trial.
- ORD conducts approximately six site visits per year of its research centers for evaluation of performance and determination of continued funding. It also investigates allegations of variations from prescribed research policies approximately three times per year.
- The Nuclear Regulatory Commission conducts site visits of its low-level radiation licensees (including VA medical centers and research facilities) every three years. When human studies are conducted under the license, NRC site visitors review human ethical standards and compliance.
- The ACOS-R performance plan, used as a self-appraisal tool, has been sent to all ACOS-Rs for commentary and evaluation of operational vulnerabilities. Data from this survey are currently being analyzed.

Additional measures to assess and ensure systemwide adherence with regulations and policies for the protection of human research subjects are under development and will be forthcoming in the near future.

10. Any other problems in any VA medical research programs, including a full report of all FDA, NRC, OSHA, DEA, OSC, MSPB, EEOC, OPRR and any other federal agency involvement with VA research projects, personnel and subjects for the past five years.

Answer:

VA has been able to gather the information described above from FDA, NRC and OPRR. Information held by the other agencies generally is in formats that do not easily lend themselves to isolating specific problems within VA research programs at medical centers. However, each agency has a reporting requirement to the individual medical centers in the event any problems come to their attention. In order to obtain the most complete information with respect to these other agencies, we plan to conduct a survey of each medical center, requesting from them the type of information requested. Results of the survey will be provided to the Committee.

Food and Drug Administration

VA asked the FDA Consumer Safety Office of the Clinical Investigation Branch, Division of Scientific Investigation, to provide information regarding FDA investigations of VA research studies involving the use of Investigational New Drugs (IND) in support of new drug applications. For present considerations, there are two types of FDA investigations: (1) study-oriented investigations; and (2) investigator-oriented investigations. Causes for an investigator-oriented inspection include, among other things: the clinical importance of the study; concerns by sponsors over the performance of an investigator; and complaints by study subjects. Since 1993, there have been 10 investigator-oriented investigations of VA projects by FDA. FDA did not provide VA with the reason for any of the investigations. They did, however, provide VA with the findings of those investigations.

In one case, FDA found no deficiencies in the conduct of the study. Of the remaining nine, FDA sent a letter to each VA investigator regarding a deficiency or deficiencies in a study. The deficiencies noted are as follows:

- Inadequate patient consent form (5 cases);
- Inadequate drug accountability (1 case);
- Failure to adhere to protocol (6 cases);
- Inadequate and inaccurate records (3 cases);
- Failure to report adverse reactions (1 case);
- Miscellaneous (1 case).

No deficiencies were identified in 1998, nor to date in 1999, in any VA program. In addition, FDA did not classify any of the reports as having problems serious enough to warrant official action by the Agency.

Nuclear Regulatory Commission

To monitor compliance with NRC regulations at VA medical centers, the National Health Physics Program was established at the Ann Arbor VAMC in conjunction with the Office of the Director of VHA's Nuclear Medicine and Radiation Safety Service, Diagnostic Services Strategic Healthcare Group. NHPP/Nuclear Medicine and Radiation provided the following information regarding VA performance in radiation protection, especially when research subjects are involved.

The NRC issues a variety of licenses to institutions to use radioactive byproduct material for medical and research purposes. Generally, licensees are site-visited by NRC inspectors every three years. Attachment 1 is a summary of data on VA compliance with NRC regulations since 1994. As is demonstrated by the summary, no VA has ever been reported, during that period, to have a Severity Level 1 or 2 violation (levels that could involve danger to human health). During that same period no VA medical center has ever been cited by NRC for human research violations. Currently, the average number of violations that NRC finds upon a given inspection of a VA licensee is less than one. Additionally, the number of Level 3 violations has declined since 1994 by about 75%.

Office for Protection from Research Risks

Currently, OPRR has four open compliance investigations of or related to VA research:

Greater Los Angeles Health Care System – On March 22, 1999, OPRR notified VA of its intent to deactivate MPA-1087.

Cincinnati, OH – This OPRR investigation involves the research assurances of the University of Cincinnati, Shriners Hospital, and Cincinnati VAMC, which share a common MPA held by the university. In addition, ORD takes every allegation potentially concerning VA scientists and research projects seriously. On April 21, an external expert team from VA Headquarters will review and verify results from ongoing internal audits of VA research at the Cincinnati VAMC.

Tampa, FL – This OPRR investigation involves an MPA to the University of South Florida (USF), which has an Inter-Institutional Agreement (IIA) with the James A. Haley VAMC. The IIA between USF and VA allows USF IRBs to review HHS-funded studies awarded to USF, but carried out either completely or partially at James A. Haley VAMC. The preliminary allegation involves a USF faculty person who is a part-time VA employee. At this time these allegations appear to involve neither VA-funded research nor research involving veterans. Currently, ORD does not have an active investigation at James A. Haley VAMC. However, VA is in communication with OPRR concerning this matter.

Philadelphia VAMC – A recent allegation against a cardiology researcher at the VAMC in Philadelphia is being investigated by OPRR. ORD does not currently have an active investigation at the Philadelphia VAMC. Again, VA is in communication with OPRR concerning this matter.

11. Any other complaints, claims or legal actions by veterans, family members or VA employees involving VA research for the past five years.

Answer:

The VA Office of General Counsel requested that Regional Counsel Offices review their records for any complaints, claims or legal actions as described above. Attached is a list of Tort Claims arising from VA research projects, 1994-1999 (Attachment 2). A total of 12 claims had been filed. Nearly half of the claims have been denied, with the remainder having been settled or under litigation. Information contained in Attachment 2 is protected by confidentiality provisions and is considered sensitive.

12. What safeguards exist to protect inappropriate patients from being used in medical research.

Answer:

There are two major safeguards to protect inappropriate patients from being used in medical research: a) scientific review; and b) human studies review.

All research conducted in VA must undergo scientific review prior to any further action to initiate the protocol. All research proposals are initially reviewed by the local (R&D) Committee situated within VA medical center research offices. With respect to scientific review, it is axiomatic that all research on human volunteers must contain well-defined criteria for the inclusion and exclusion of subjects from the proposed study. Good clinical research cannot be conducted in the absence of adherence to this fundamental principal.

Generally, all research proposals may not proceed without approval by the R&D Committee. As a part of the review conducted by the R&D Committee, human studies are referred to the Human Subjects Subcommittee (HSS) (the institution's IRB) for a review of the proposal with respect to all elements of general human bioethics, the standards of federal regulations for federally sponsored or regulated research embodied in the Common Rule, and in Food and Drug Administration regulations, as appropriate. Additionally, the HSS must apply the human research policies of VA that are embodied in VA Policy Manual M3, Pt.1, Ch. 9. These latter policies meet, and in many cases exceed, the requirements of the federal Common Rule. Any research project conducted in a VA facility, or supervised by a VA principle investigator, is considered to be VA research, and therefore subject to the provisions of the Common Rule and supplemental VA research policies.

One element of a HSS review is consideration of the risks of study to volunteers and a determination of relationship of risks to benefits to be derived from the study. Assessment of study risks requires clear definitions of inclusion and exclusion criteria. The risk of study participation is almost always a function of the inclusion criteria. The HSS cannot approve a human study in the absence of a clear description of risks and benefits. The R&D Committee cannot approve a human research project that has not been approved by the HSS.

When approved by the R&D Committee, a significant number of human study protocols are submitted to funding agencies and undergo further competitive peer review. Peer reviewers, although examining the science of the project in great detail, are also bound to identify any potential problems with respect to subject protection. A peer review panel may recommend to funding officials that funding be denied or postponed if there are any bioethical concerns. In regard to a specific human study project, no VA official can override a negative decision of the reviewing HSS. Conversely, a higher-level VA official does have the authority to override a positive decision.

The system of review and checks and balances within the review process is designed to ensure that subjects appropriate for participation in a human study are included, and those that are not are excluded. Ultimately, it is the investigator who is

bound by rules and ethics to follow his/her own protocols inclusion/exclusion criteria. The HSS, under provisions of the Common Rule, must conduct continuing review of research that it has approved at intervals appropriate to the risk, but no less than once per year. It shall have the authority to observe, or have a third party observe, the consent process and the research at any time (56 FR 28003, incorporated into 38 CFR 16 and approved by the Office of Management and Budget under Control Number 9999-0020).

Besides these safeguards, more specific checks are provided by VA research policies.

- Data checks are performed during the conduct of all multi-site trials to ensure the inclusion/exclusion criteria are rigorously followed prior to placement of a volunteer into a study;
- Audits of drug studies by the VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center for Good Clinical Practice;
- Ongoing audits for compliance with standard operating procedures for VA and industry-sponsored trials;
- Annual local IRB reviews for progress reports;
- FDA oversight for trials supporting new drug or new device applications; and
- NRC oversight for human studies involving ionizing radiation.

13. All applicable VA policies and regulations governing both informed consent and Institutional Review Boards in VA medical research.

Answer:

There are numerous policies and regulations governing VA research involving human subjects. VA policies and regulations exceed those required across the government by the Common Rule agencies, including HHS.

Federal Regulations

VA is one of 17 federal agencies that are co-signatories to the Federal Policy for the Protection of Human Subjects (56 FR 28003). VA has incorporated the Common Rule into its own regulations, contained at 38 CFR 16. For federally funded research VA is legally bound to adhere to the regulations articulated within 38 CFR 16, including detailed descriptions of informed consent and the structure and responsibilities of Institutional Review Boards.

VA considers all research at a VA facility as VA research, even if direct funding costs do not derive from federal funds. This would be the case, for example, if a pharmaceutical company were funding research at a VA medical center.

Finally, VA has gone further in protecting human research subjects than is provided by either the Common Rule or FDA regulations. Despite repeated calls that the federal government address the issue of compensating research injuries, VA is the only agency that has amended its Regulations (38 CFR Section 17.85) to provide for compensation to persons injured as a result of participation in VA research. (The only other agency to have additional regulatory protections is HHS, which has subparts to address research involving children, prisoners, and pregnant women and fetuses.)

For human studies conducted at a VA in support of a new drug or device application to the FDA, the human studies component also comes under the authority of FDA regulations for the protection of human subjects in research (21 CFR 50 and 21 CFR 56). Because 38 CFR 16 regulates all federally sponsored research at VA – and because 21 CFR 50 and 21 CFR 56 cover all VA research in support of a new drug or device application – when VA researchers are engaged in research that supports a new drug or new device application, the researchers must comply with both sets of regulations.

VA and FDA are partners in a memorandum of understanding that enhances the communications between FDA and VA with respect to a number of FDA requirements. In particular, FDA has agreed to notify VA medical center directors of investigative findings relating to a particular study, and advise VA of any violations resulting from investigations into the performance of clinical investigators or Human Studies Subcommittees (HSS/IRBs) associated with VA.

VA Policies

In 1992, shortly after the establishment of the federal Common Rule, VA issued a revised policy incorporated into its policy manual M3, Pt.1, Ch.9 (Attachment 3). This Chapter is called "Requirements for the Protection of Human Subjects".

Chapter 9 incorporates the provisions of the Common Rule (38 CFR 16), and FDA regulations 21 CFR 50 and 56. In addition, Chapter 9 explains how the provisions of these regulations are to be implemented in the specific context of VA research at VA medical centers. In some instances, M3, Pt. 1, Ch.9 exceeds other regulatory requirements. For example, the Common Rule is relatively silent on the issue of informed consent in persons with impaired decision-making capacity, only pointing out the possibility of consent by a legally authorized representative. In contrast M3, Pt.1, Ch.9, sec.12 is devoted in detail to "Research on Human Subjects with Surrogate Consent". It describes conditions under which a researcher may seek surrogate consent for an individual with impaired decisionmaking capacity.

Because VA has a large program in cooperative trials for the study of new drugs, therapies and devices, in 1997, the VA Cooperative Studies Program developed detailed guidelines, "Cooperative Studies Program: Guidelines for the Planning and Conduct of Cooperative Studies" (Attachment 4). A major part of these guidelines is devoted to describing the requirements for protocol review and informed consent. These guidelines derive from 56 FR 28003 (the Common Rule), 38 CFR 16, and the VA policy manual M3, Pt.1, Ch.9.

VA Research with Radionuclides

1. Scope

Total # VA NRC licenses (clinical nuclear medicine and research): 130

Licenses permitting biomedical research: 78

performing human radionuclide research¹: 35

2. NRC Compliance History (CY94-CY98; biomedical research licenses)

a. NRC inspections: 203

• Violation Type² and rates (ave. # / insp.)

	<u>CY94</u>	<u>CY95</u>	<u>CY96</u>	<u>CY97</u>	<u>CY98</u>
Severity Level 3	2.3	0.5	0.5	1.1	0.6
Severity Level 4	.03	.02	.03	.08	.02

Notes

1. For the purposes of this report, human radionuclide research is defined as a study of any of the following four types:

- a. RDRC study: A Radioactive Drug Research Committee study (RDRCs are approved by the FDA);
- b. IND: A use under an Investigational New Drug protocol;
- c. Approved radioactive drug used in research protocol: those approved, routine studies used as a diagnostic component in a research study (e.g., Thallium-201 test used as a diagnostic procedure in a VA cooperative study to evaluate patency of heart grafts);
- d. IDE evaluation: Investigation device evaluation, similar to b. above.

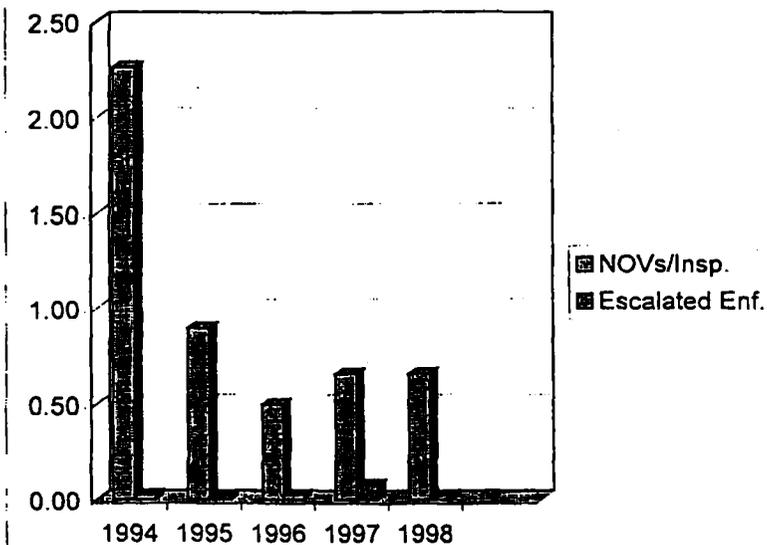
2. Violation Types: NRC Severity Levels range from 1 to 4, 1 being most significant. The actual NRC definitions are: Severity Level 3 - violations are cause for significant regulatory concern; Severity Level 4 - Violations are less serious but are of more than minor concern; i.e., if left uncorrected, they could lead to a more serious regulatory violation. Examples: SL 3- Failure to control access to radioactive materials, failure to report misadministration of therapeutic dose to patient; SL 4 - Isolated failure to review quality management program involving therapeutic uses, use of improperly calibrated equipment. *No VA has ever been cited for a SL 1 or 2 violation.*

We have no reason to believe VA violations are no different from other licensees. VA incidence rates of SL 3 type violations are less than that of the Department of the Navy, a comparable class of licenses; few other license classes are structured similarly to the VA - i.e. medium nuclear medicine and small research programs.

Additional Comments

• *No VA has ever been cited by NRC for human research violations.*

NRC Notices of Violation (NOVs) per VA Facility Inspection



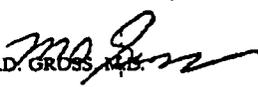
Data:	CY	1994	1995	1996	1997	1998
Inspections		38	48	38	38	41
NOVs		86	43	19	25	27
NOVs/Insp.		2.26	0.90	0.50	0.66	0.66
Severity Level 3 rate		0.03	0.02	0.03	0.08	0.02

DEPARTMENT OF
VETERANS AFFAIRS

Memorandum

Date: May 19, 1998
From: Program Director, Nuclear Medicine Service, Diagnostic Services SHG (115B)
Subj: Fact Sheet, Clinical Research with Radioactive Materials
To: (11) ATT: T. Holohan, M.D.

1. Attached is a fact sheet that may be assistive to both medical and non-medical staff especially management in understanding:
 - the distinction between clinical research and the scope of medical practice including clinical use of radioisotopes
 - the various VA approval processes when undertaking clinical research with radioactive materials.
2. The on-going brouhaha at the Philadelphia VA and past allegations and innuendo regarding improper experimentation with radioactive materials has clearly demonstrated that some guidance and reference materials would be helpful to the field.
3. I have circulated this to both the Research Service - Timothy Gerrity, Ph.D. and Public Health and Environmental Hazards - Neil Otchin, M.D. and received their comments and concurrence.
4. I am uninformed regarding any new or continuing concerns that the release of this issue paper might influence/compromise.
5. Clarifications may be directed to me at (734) 761-7885.


M.D. GROSS, M.D.

ATT: 1

**DEPARTMENT OF VETERANS AFFAIRS (VA)
VETERANS HEALTH ADMINISTRATION (VHA)**

**CLINICAL RESEARCH WITH RADIOACTIVE MATERIALS IN
THE DEPARTMENT OF VETERANS AFFAIRS**

I. Background

Medical research is an important component of the mission of the Department of Veterans Affairs (VA). Research conducted in VA facilities has contributed much to the understanding and treatment of disease. VA researchers have achieved the highest accolades for research excellence and many are internationally recognized for their contributions. Radioisotopes and labeled compounds (radiopharmaceuticals) play an important role in medical research. These agents allow noninvasive, remote measurements of physiologic and pathophysiologic processes and have been applied throughout virtually all medical specialties in clinical and research applications.

The process for approval of the use of radioisotopes and radiopharmaceuticals in man has evolved into a somewhat complex marriage of intra and extra VA committee and agency approval processes. Recent events in VA concerning the conduct of human research with radioactive materials has raised many questions concerning the approval process(es) in VA and the role of other governmental agencies in the regulation of these activities. This fact sheet will outline the approval process for use of radioactive materials in human research. In addition it will define the scope of medical practices that include clinical use of radioisotopes and how this differs from that of clinical research.

II. Regulation of Radioactive Materials in Human Research

A. Food and Drug Administration (FDA)

FDA is responsible for assuring the safety and efficacy of radioisotopes and radiopharmaceuticals used in humans. A comprehensive process is employed to evaluate drugs (to include radiopharmaceuticals) to assure their safety and clinical efficacy. This process is referred to as a new drug application (NDA) and is usually, but not exclusively, initiated by radiopharmaceutical manufacturers. FDA approves radiopharmaceuticals for particular clinical indications. FDA approved indications are enumerated in the package insert materials supplied by the manufacturer. FDA also approves projects using radioisotopes or radiopharmaceuticals submitted by physicians as investigational new drug (IND) applications (Form FDA-1571) subject to rigorous FDA review. Once approved by FDA, IND applications must be reviewed by VA facility Research and Development (R&D), Subcommittee on Human Experimentation (URB) and Radiation Safety Committee (RSC) for local approval (see below).

An alternative approval process exists for research radioisotopes and radiopharmaceuticals that meet stringent requirements of no biologic effect and limited radionuclide dosimetry. This pathway is through a local VA facility FDA-sanctioned committee, the Radioactive Drug Research Committee (RDRC) (see below).

B. Nuclear Regulatory Commission (NRC)

NRC is responsible for regulating the safe use of reactor-produced radioisotopes (and thus certain radiopharmaceuticals). A complex licensing process exists that mandates users to comply with regulations concerning receipt, storage, use (both clinical and research) and disposal of radioactive materials to demonstrate compliance with licensing conditions and regulations. NRC conducts unannounced inspections at all medical facilities licensed to use radioactive materials. Medical facilities that conduct research with radioactive materials must comply with 10 CFR Parts 19, 20 and 35. The Radiation Safety Committee (RSC) represents NRC at each medical facility. The RSC is responsible for reviewing research proposals for safety and scientific quality.

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 Clinical Research with Radioactive Materials in
 the Department of Veterans Affairs

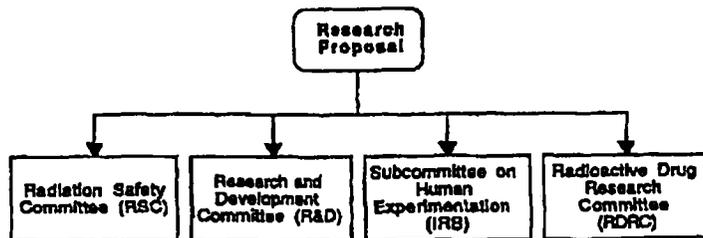
III. Regulation of DVA Human Research with Radioactive Materials

A. Background

A licensee may conduct research involving human subjects using ionizing radiation provided that the research is conducted, funded, supported, or regulated by another Federal Agency which has implemented the "Federal Policy for the Protection of Human Subjects". At a minimum, an investigator must obtain informed consent from the research subjects and obtain prior review and approval of the research activities by an "Institutional Review Board" in accordance with the meaning of these terms as defined and described in the "Federal Policy for the Protection of Human Subjects" (16 CFR 31.6).

No matter how small the amount of radioactivity, research involving administration of a radioactive drug(s) or sources of ionizing radiation to human subjects shall not be permitted unless all applicable medical facility committees conclude that scientific knowledge and/or clinical benefit is likely to result from the research study. Research protocol(s) must be based upon a sound rationale derived from appropriate basic science investigations or published literature and be of sound design such that information of scientific value or clinical benefit may result. The radiation dose must be sufficient but no greater than necessary to accomplish the goal(s) of the research proposal. The projected number of subjects must be sufficient, but no greater than necessary for the purposes of the study. The number of subjects must also reflect that the study is intended to obtain basic research information or for therapeutic, diagnostic or similar purposes or to determine the safety and effectiveness of a drug in humans (i.e. a clinical trial).

Approval from appropriate medical facility committees is mandatory prior to initiating research involving human subjects. The flow chart below identifies the multiple VA medical facility committees involved with review and approval of radiopharmaceuticals and/or sources of ionizing radiation for research in human subjects.



Flow Chart 1

1. Studies defined below as "A", "B", "C", & "D" are reviewed/approved by the Radiation Safety Committee (RSC), Research and Development Committee (R&D), and the Subcommittee on Human Experimentation (IRB).
2. Studies defined below in section c as "C" are additionally reviewed/approved by the Radioactive Drug Research Committee (RDRC).

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Research Study Identification:

- a. "A" Well established radioactive material use in humans, for which a New Drug Application (NDA) has been filed with FDA.
- b. "B" A use for which an Investigational New Drug (IND) application has been approved by FDA.
- c. "C" A research use to obtain basic research information regarding the metabolism (including kinetics, distribution, and localization) of a radioactive drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic or similar purposes or to determine the safety and effectiveness of the drug in humans (21 CFR 361.1).
- d. "D" The use of other sources ionizing radiation (eg., x-ray, fluoroscopy or cine).

TABLE I. HUMAN RESEARCH IN VA WITH RADIOACTIVE MATERIALS

Committee	Type of Proposed Research Project Reviewed
Research and Development (R&D)	A, B, C, D
Radiation Safety Committee (RSC)	A, B, C, D
Human Experimentation Committee (HEC)	A, B, C, D
Radioactive Drug Research Committee (RDRC)	C

B. Committee Review Functions

1. Radiation Safety Committee (RSC)

In VA the RSC is responsible for ensuring the safe use of all forms of ionizing radiation in accordance with all applicable regulations (NRC, EPA, DOT, FDA & VA). Membership includes a chairman (usually a nuclear medicine specialist, radiologist, or senior medical research staff member with experience in the use of radioactivity in both clinical and research applications), the radiation safety officer (RSO) and representation from hospital administration, patient care (nursing) and other user services to include nuclear medicine, radiology, radiation oncology, research and internal medicine (cardiology, pulmonary, gastroenterology) as members of the committee. The RSC represents NRC at the medical facility. The RSC chairman and RSO are specifically named in each medical facility's NRC license. The NRC inspects medical facilities compliance with 10 CFR, which includes the use of radiopharmaceuticals in man. The basic elements reviewed by the RSC for research projects are:

- a. training and experience of the investigator
- b. training and experience of all individuals handling radiotopes or ionizing radiation
- c. physical form and amount of radiotope or form of ionizing radiation
- d. physical space for the use of the radiotope or ionizing radiation
- e. proposed use of the radiotope or ionizing radiation
- f. safety procedures for the safe use of the radiotope or ionizing radiation
- g. physical form and amount of waste to be generated

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2. Research and Development Committee (R&D)

All proposed research studies performed at VA facilities must undergo review by a local R&D Committee to assure the scientific quality of the study and that a research project will not adversely affect medical facility clinical or research facilities or personnel. Representation is usually broad with members from many medical specialties and hospital administration.

The R&D Committee is charged with the responsibility to review the scientific, administrative and budgetary aspects of all research proposals. The basic elements reviewed by the R&D Committee for research projects are:

- a. brief description of the research project (abstract)
- b. budget
- c. rationale for the research project
- d. research problem or question to be answered by the research project
- e. specific aims or objectives of the research project
- f. background information pertinent to the research project
- g. preliminary data by investigator
- h. general methods to be used in the research project
- i. experimental plan of the research project
- j. data analysis/interpretation

3. Subcommittee on Human Experimentation (IRB)

Every VA medical facility must have an IRB. The IRB is responsible for reviewing proposed human research in terms of medical facility commitments and policies, applicable law and standards of professional conduct and practice. Membership must include a broad range of staff knowledgeable in these areas. The IRB is charged with the responsibility to approve all research activities in human subjects (Manual M-3, Part I Chapter 9 and 21 CFR Part 36). The basic elements reviewed by an IRB for all proposed research projects are:

- a. rationale of the proposed research project
- b. minimization of risks
- c. reasonable risk/benefit ratio
- d. equitable selection of subjects
- e. securing and documenting informed consent
- f. monitoring safety of research subjects
- g. privacy and confidentiality of research subjects
- h. protection of vulnerable research subjects
- i. documentation of all the above by an appropriate method of informed consent (21 CFR Part 30 Subpart B)

4. Radioactive Drug Research Committee (RDRC)

The RDRC reviews all uses of radioactive drugs in humans for the purposes of research that have not been previously approved by FDA that meet stringent requirements (see below). The proposed use of radioactive drug(s) or any x-ray procedure used in conjunction with the study must be in accordance with FDA regulations (21 CFR Part 361). RDRC membership is specified in 21 CFR 361 and is to include a clinician with experience in the research application of radiopharmaceuticals, medical facility RBC, a biologist or chemist familiar with drug formulation and representatives from medical center administration and user services. FDA approves the credentials of each member of the RDRC. The RDRC represents the

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FDA at the medical facility. The facility is subject to unannounced FDA inspections of EDRC activities. The elements reviewed by a EDRC for research projects that fall under EDRC purview are:

- a. investigator qualifications
- b. Econsent for the use of the radioisotope
- c. intent to pursue research (defined in 21 CFR Part 361)
- d. lack of pharmacologic effect(s)
- e. selection of research subjects
- f. provisions for the reporting of adverse reactions
- g. radiation dosimetry
- h. quality control of the radioactive drug
- i. concurrence of approval by IRB

IV. Reporting Requirements (Table 2)

A. FDA

1. Annual Reports

Radioactive drugs used for research purposes in humans as described in 21 CFR Part 361 are approved on a per project basis by the Radioactive Drug Research Committee (RDRC). Each RDRC must submit an annual report to FDA on or before January 31st. The annual report must include the names and qualifications of the committee members and any consultants used by the RDRC (FDA Form 2914). The annual report to FDA also includes a summary report for each project conducted during the preceding year (FDA Form 2915). The RDRC chairman is responsible for the timely review of annual membership and research study summaries to FDA.

2. Adverse Reactions

Human research studies involving the use of radioactive drugs are subject to regulations regarding reporting of adverse reactions. All adverse reactions or effects associated with the use of a radioactive drug in a research study must be reported to the EDRC (if the study is conducted under EDRC aegis), the RSC and the Chief, Research Service. If applicable the chairman of the EDRC is responsible for notifying FDA. Since radioactivity is involved, the RSC chairman and the medical facility RSO should also be notified of any adverse reactions.

B. NRC

Human research studies are subject to NRC regulations regarding the misadministration of ionizing radiation. Specific notification, reporting and documentation of misadministrations and undesirable events must be followed (10 CFR Part 35.53). The RSC chairman and RSO are responsible for meeting these reporting requirements.

C. VA

Incidents involving beneficiaries (VA patients and/or research subjects) which occur at a medical facility must be promptly investigated and reported. An incident is defined as "any instance which causes or has the potential to result in harm to a beneficiary." An adverse reaction to a radioisotope or radiopharmaceutical is an example of an incident for which VA Form 10-2633, "Report of Special Incident Involving a Beneficiary" must be made.

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TABLE 2. COMMITTEE REPORTING REQUIREMENTS FOR HUMAN RESEARCH

COMMITTEE	MEETS	REPORTS LOCAL	REPORTS NATIONAL	INSPECTIONS
R&D	Monthly	CEB ^a	VA	Medical Center T Quality P Program (JCAHO) ^c
IRB	Monthly	R&D (CEB)	VA	FDA (Announced)
RSC	Quarterly & Annually	CEB		NRC (Unannounced)
RDRC	Quarterly & Annually	RSC (CEB)	FDA ^d NRC ^d	FDA (Unannounced) NRC (Unannounced)

^a Clinical Executive Board

^b Total Quality Improvement

^c Joint Commission Accreditation Hospital Organization

^d Misadministration or Adverse Reaction

V. Clinical Scope of Practice vs. Clinical Research

Both FDA and NRC acknowledge that there are clinical circumstances where deviations (i.e. off label) from approved uses of radiopharmaceuticals are necessary in the routine management of patients. Criteria for exempting an "off label" use of an approved radioactive drug from IND requirements are: (a) no significant increase in patient risk and (b) an intention to develop a new indication(s) for use of the radioactive drug (e.g., a clinical research project). These provisions allow for changes to be made in the preparation, route of administration or indication(s) for use of a radiopharmaceutical that deviate from approved methods of preparation, route of administration or indication(s) in the course of medical management of a patient deemed necessary for patient care. The intent of the deviation(s) from an approved use of a radiopharmaceutical is to obtain information important in the clinical management of a patient. The intent of these "off label" uses is not to conduct a clinical research trial. Deviations from an approved use of a radiopharmaceutical occur after consultation between a referring physician and a nuclear medicine or radiology physician. A written requisition to perform an imaging procedure has been made by a credentialed and privileged referring physician to a credentialed and privileged nuclear medicine or radiology physician for the express purpose of obtaining imaging information necessary in clinical management. This is broadly defined as the scope of clinical practice. The proposed procedure is discussed with the patient (oral informed consent). Deviations from approved uses are documented in the prescription for the radiopharmaceutical that is initiated by the nuclear medicine or radiology physician. A formal description of the indication(s) for the procedure, reason(s) for deviation(s), methods (preparation, dose and route of administration), description of the images, scan interpretation and recommendations as a result of the procedure become part of the permanent medical record of the patient. Conversely, an IND would need to be submitted to FDA for new radiopharmaceuticals or alternative uses of established radioactive drugs used for clinical research purposes as a prelude to medical facility IRB, RSC and R & D committee approval.

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VI. References

Title 10, Code of Federal Regulations

- Part 19* **Notices, Instructions, and Reports to Workers; Inspections**
Part 20 **Standards for Protection Against Radiation**
Part 30 **Rules of General Applicability to Domestic Licensing of Byproduct Material**
Part 33 **Specific Domestic Licenses of Broad Scope for Byproduct Material**
Part 35 **Medical Use of Byproduct Material**
Part 49 **Federal Policy for the Protection of Human Subjects**

Title 21, Code of Federal Regulations

- Part 30* **Protection of Human Subjects**
Part 36 **Institutional Review Boards**
Part 207 **Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution**
Part 211 **Current Good Manufacturing Practice for Finished Pharmaceuticals**
Part 310 **New Drugs**
Part 312 **Investigational New Drug Application**
Part 314 **Application for FDA Approval to Market a New Drug or an Antibiotic Drug**
Part 361 **Prescription Drugs for Human Use Generally Recognized as Safe and Effective and Not Misbranded: Drugs Used in Research**

"General Requirements for Informed Consent", Federal Policy for the Protection of Human Subjects, Federal Register, June 18, 1991.

VHA Manual M-3, Part I

VA Policy 10-9012 Investigational Drugs

Information contained in Attachment 2 is protected by confidentiality provisions and is considered sensitive.

Please do not print as part of the hearing record.

October 30, 1992

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Chapter 9

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CHAPTER 9. REQUIREMENTS FOR THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH

9.01 INTRODUCTION

The recent publication of the Federal Policy for the Protection of Human Subjects (56 FR 28001-32, June 18, 1991) meets a widely recognized need for uniformity among Federal departments and agencies in ensuring protection of the rights and welfare of individuals involved as subjects of research under Federal auspices. This policy is a result of several years effort to formulate a uniform policy that would eliminate unnecessary regulation and promote increased understanding and ease of compliance by institutions, organizations, and individuals who conduct Federally supported or regulated research involving human subjects.

9.02 PURPOSE

This chapter implements 38 CFR (Code of Federal Regulations) 16. The policies and procedures set forth in this chapter supersede all previous VA (Department of Veterans Affairs) directives related to the protection of human subjects in research.

9.03 POLICY

a. VA is one of the 16 departments and agencies that have agreed to follow the Federal Policy for the Protection of Human Subjects, effective August 19, 1991. This policy is incorporated in 38 CFR 16.

b. With the exception of categories listed in appendix 9A, the provisions of this chapter apply to all research involving human subjects conducted completely or partially in VA facilities, including research funded from extra-VA sources and research conducted without direct funding.

c. Investigators receiving support from such Federal agencies as the National Institutes of Health must meet the human subjects requirements of the funding source. However, since these agencies are also regulated by the Federal Policy for the Protection of Human Subjects, their human subjects requirements will not differ importantly from the requirements expressed in this chapter.

9.04 DEFINITIONS

The following terms, defined in 38 CFR 16.12, are defined more specifically for the purposes of this chapter

a. **Legally Authorized Representative.** A legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. For the purposes of this chapter, a "legally authorized representative" includes not only persons appointed as health care agents under DPAHC (Durable Powers of Attorney for Health Care), court appointed guardians of the person but also next-of-kin in the following order of priority:

- (1) Spouse.
- (2) Adult child (18 years of age or older).

(3) Parent.

(4) Adult sibling (18 years of age or older).

b. Human Subject. The definition of human subject provided in the Federal Policy is expanded to include investigators, technicians, and other assisting investigators, when they serve in a "subject" role by being observed, manipulated, or sampled.

c. IRB (institutional review board). IRB is defined in the Federal Policy as an institutional review board established in accord with and for the purposes expressed in this policy. For the purposes of this chapter, the Subcommittee on Human Studies of the Research and Development Committee constitutes an IRB. Therefore, IRB will be used to refer to either the Subcommittee on Human Studies and any affiliated university IRB that may service a VA facility.

9.05 AUTHORITY

a. Statutory provisions for protection of VA patient rights: 38 U.S.C. (United States Code) Sections 7331 through 7334.

b. VA regulations pertaining to protection of patient rights: 38 CFR Sections 17.34 and 17.34a.

c. VA regulations pertaining to rights and welfare of patients participating in research: 38 CFR 16 (Federal Policy for the Protection of Human Subjects).

d. DHHS (Department of Health and Human Services) regulations pertaining to rights and welfare of patients participating in research supported by DHHS: 45 CFR 46.

e. FDA (Food and Drug Administration) regulations pertaining to rights and welfare of patients participating in research involving investigational drugs and devices: 21 CFR parts 50 and 56.

9.06 RESEARCH EXEMPT FROM THE PROVISIONS OF THIS CHAPTER

a. Exempt categories. Research activities in which the only involvement of human subjects will be in one or more of the minimal risk categories listed in appendix 9A of this chapter are exempt from the requirements of this chapter. An IRB must approve the exempt status.

b. Determination of exemption. An investigator wishing to have a research proposal exempted from IRB review shall present a request in writing, along with the research proposal, to the R&D (Research and Development) Committee. The request will be justified by showing that the proposed research falls into one or more of the categories listed in appendix 9A.

c. Documentation of Research and Development Committee action. The Research and Development Committee or its designee shall review all requests for exemption in a timely manner, record its decision along with the basis of the decision, and communicate the decision in writing to the investigator.

9.07 MEDICAL CENTER RESPONSIBILITIES

a. Establishing an IRB. Every VA medical center shall either:

(1) Have or establish an IRB (Subcommittee on Human Studies).

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(2) Arrange for securing the services of a Subcommittee on Human Studies from another VA facility, including the Eastern and Western R&D Offices.

(3) Arrange for securing the services of an IRB established by an affiliated medical or dental school:

(a) If the medical center chooses to use the services of an affiliated university IRB, VA interests will be adequately represented, usually by the inclusion of at least one VA employee with scientific expertise on the IRB.

(b) An IRB established by an affiliated medical or dental school must agree to comply with the provisions of 38 CFR 16.

(c) When VA utilizes an IRB established by an affiliated medical or dental school, the informed consent forms that will be used by prospective veteran-subjects must include a statement in compliance with paragraph 2a(12) of appendix 9C.

b. Operating an IRB. Every VA medical center will provide (if needed) meeting space and sufficient staff to support the IRB's review and record keeping duties. The authorities and responsibilities of IRB's are described in paragraph 9.09.

9.08 IRB COMPOSITION

a. Number and Qualification of Members

(1) Each IRB will have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the medical center.

(a) The IRB will be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of:

1. Race.
2. Gender.
3. Cultural backgrounds.
4. Sensitivity to community issues and/or community attitudes.

(b) The IRB will:

1. Promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.
2. Possess the professional competence necessary to review specific research activities.

(2) The IRB, to be able to ascertain the acceptability of proposed research in terms of medical center commitments and policies, applicable law, and standards of professional conduct and practice, will, therefore, include persons knowledgeable in these areas.

b. Group Heterogeneity

(1) Every nondiscriminatory effort will be made to ensure that no IRB consists

entirely of men or entirely of women, including the medical center's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender.

(2) No IRB may consist entirely of members of one profession.

c. Scientific/nonscientific Members

(1) Each IRB will include at least one member whose primary concerns:

(a) Are in scientific areas.

(b) Are in nonscientific areas.

(2) These members will be selected primarily to reflect the values of the community with respect to the rights and welfare of human research subjects.

(3) To serve as part of the IRB, it is recommended that members of the community be considered, such as:

(a) Clergypersons.

(b) Attorneys.

(c) Representatives of legally recognized veterans organizations.

(d) Practicing physicians.

d. Non-VA Members. Each IRB will include at least one member who is not otherwise affiliated with the medical center and who is not part of the immediate family of a person who is affiliated with the medical center.

e. Conflict of Interest. No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

f. Ad Hoc Members. An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

9.09 IRB AUTHORITY AND RESPONSIBILITIES

a. IRB Authority and Review Criteria. An IRB will review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this chapter. In order to approve research governed by this policy the IRB will determine that all of the following requirements are satisfied:

(1) **Minimization of Risks.** Risks to subjects are minimized:

(a) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and

(b) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

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(2) **Reasonable Risk/benefit Ratio.** Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

(a) In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapy subjects would receive even if not participating in the research).

(b) The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) **Equitable Selection of Subjects.** Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as:

- (a) Children;
- (b) Prisoners;
- (c) Pregnant women;
- (d) Mentally disabled persons; or
- (e) Economically or educationally disadvantaged persons.

(4) **Securing Informed Consent.** Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by appendix 9C.

(5) **Documenting Informed Consent.** Informed consent will be appropriately documented, in accordance with and to the extent required by paragraph 9.11b.

(6) **Monitoring Safety.** When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) **Privacy and Confidentiality.** When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data.

(8) **Protection of Vulnerable Subjects.** IRB will ensure that additional safeguards have been included in the study to protect the welfare of subjects likely to be vulnerable to coercion or undue influence, such as:

- (a) Children;
- (b) Prisoners;
- (c) Pregnant women;
- (d) Mentally disabled persons; or
- (e) Economically or educationally disadvantaged persons.

b. Notifying Investigators

(1) An IRB will notify investigators and the R&D Committee in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity.

(2) If the IRB decides to disapprove a research activity, it will include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

c. Maintaining Written Procedures for Operations. An IRB will follow written procedures:

(1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the R&D Committee.

(2) For determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and

(3) For ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazard to the subject.

d. Maintaining Written Procedures for Reporting Noncompliance. An IRB will prescribe written procedures for ensuring prompt reporting by investigators to the IRB, appropriate medical center officials, and appropriate VA Central Office officials for:

(1) Any unanticipated problems involving risks to human subjects or others;

(2) Any instance of serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and

(3) Suspension or termination of IRB approval.

e. Obtaining a Quorum for Review. Except when an expedited review procedure is used (see par. 9.10), the IRB will review proposed research at convened meetings at which a majority of the members are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it will receive the approval of a majority of those members present at the meeting.

f. Monitoring Ongoing Projects. An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and will have authority to observe or have a third party observe the consent process and its research.

g. Monitoring IRB Records

(1) **Necessary Documentation.** A medical center, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

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(a) Proposals and evaluations. Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(b) Minutes. Minutes of IRB meetings which will be in sufficient detail to show:

1. Attendance at the meetings;
2. Actions taken by the IRB;
3. The vote on these actions including the number of members voting for, against, and abstaining;
4. The basis for requiring changes in or disapproving research; and
5. A written summary of the discussion of controverted issues and their resolution.

(c) Ongoing review. Records of continuing review activities.

(d) Correspondence. Copies of all correspondence between the IRB and the investigator.

(e) Membership list

1. A list of IRB members identified sufficiently to describe each member's chief anticipated contributions to IRB deliberations, such as:

- a. Name.
- b. Earned degrees.
- c. Representative capacity.
- d. Indications of experience such as board certifications, licenses, etc.

2. Any employment or other relationship between each member and the medical center will be noted, for example:

- a. Full-time employee.
- b. Part-time employee.
- c. Member of governing panel or board.
- d. Paid or unpaid consultant.

(f) Procedures. Written procedures for conducting reviews, monitoring ongoing projects, and identifying and reporting problems with regard to compliance with the provisions of this chapter.

(g) New findings. Statements of significant new findings provided to subjects, as required by paragraph 2b(5) of appendix 9C.

(2) Record retention

(a) The records required will be retained in accordance with VHA's Records Control Schedule 10-1.

(b) All records will be accessible for inspection and copying by authorized representatives of VA at reasonable times and in a reasonable manner.

9.10 IRB RESPONSIBILITIES AND EXPEDITED REVIEW

a. **Circumstances for Expedited Review.** An IRB may use the expedited review procedure to review either or both of the following:

(1) **Eligible categories.** Any of the categories of research appearing in appendix 9B and found by the R&D Committee to involve no more than minimal risk.

(2) **Approval of minor changes.** Minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized.

b. **Procedures.** Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB.

(1) In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research.

(2) A research activity may be disapproved only after review in accordance with the non-expedited procedure.

c. **Record Keeping.** Each IRB which uses an expedited review procedure will adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

9.11 INVESTIGATOR RESPONSIBILITIES

a. **Obtaining Informed Consent.** Investigators wishing to involve human beings as subjects in research covered by this chapter will obtain legally effective informed consent of the subject or the subject's legally authorized representative. The basic elements of informed consent are listed in appendix 9C.

b. Documenting Informed Consent

(1) **Written consent form.** Except as provided in subparagraph 2b(3), informed consent will be documented by the use of a written consent form and signed by the subject or the subject's legally authorized representative. *The original signed consent form must remain in the patient's chart and copies must be retained in the experimental/research file under conditions of confidentiality.*

(2) **Two alternatives.** Except as provided in subparagraph 2b(3), the consent form may be either of the following:

(a) **Written consent document.** A written consent document that embodies the elements of informed consent required by appendix 9C. **NOTE: VA Form 10-1086, VA Research Consent Form, shall be used to meet these requirements. VA Form 10-1086.**

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may be read to the subject or the subject's legally authorized representative, but in any event, the investigator will give either the subject or the representative adequate opportunity to read it before it is signed; or

(b) Written consent document (short form). A short form written consent document stating that the elements of informed consent required by appendix 9C have been presented orally to the subject's legally authorized representative. When this method is used, there will be a witness to the oral presentation. This process includes the following:

1. The IRB will approve a written summary of what is to be said to the subject or the representative.
2. Only the short form itself is to be signed by the subject or the representative.
3. The witness will sign both the short form and a copy of the summary, and the person actually obtaining consent will sign a copy of the summary.
4. A copy of the summary will be given to the subject or the representative, in addition to a copy of the short form.

(3) Waiver of requirement. An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(a) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(b) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding research. (Approved by the Office of Management and Budget under Control Number 8999-0020.)

9.12 RESEARCH ON HUMAN SUBJECTS WITH SURROGATE CONSENT

a. Policy. Under appropriate conditions, investigators may obtain informed consent from the legally authorized representative of patients (surrogate consent).

(1) Such consent may be obtained not only from health care agent appointed by the patient in a DPAHC or similar document, court-appointed guardians of the person but also from next-of-kin in the following order of priority:

- (a) Spouse.
- (b) Adult child (18 years of age or older).
- (c) Parent.
- (d) Adult sibling (18 years of age or older).

(2) Such consent may be requested and accepted only when the prospective research participant is incompetent as determined by two VA physicians, after appropriate medical evaluation and there is little or no likelihood that the patient will regain competence within a reasonable period of time, or as established by a legal determination.

(3) This policy is designed to protect patients from exploitation and harm and, at the same time, make it possible to conduct essential research on problems that are unique to patients who are incompetent (e.g., a study of treatment options for comatose patients can only be done with incompetent subjects).

b. **Criteria for IRB Approval.** Before incompetent persons may be considered for participation in any VA research, the IRB must find that the proposed research meets all of the following conditions:

(1) **Only incompetent patients suitable.** Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or subjects. Incompetent persons must not be subjects in research simply because they are readily available.

(2) **Favorable risk/benefit ratio.** The proposed research entails no significant risks, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people will not be subjects of research which imposes a risk of injury unless that research is intended to benefit the subject and the probability of benefit is greater than the probability of harm.

(3) **Voluntary participation.** Although incompetent to provide informed consent, some patients may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

(4) **Well-informed representatives.** Procedures have been devised to assure that participants' representatives are well-informed regarding their roles and obligations to protect incompetent subjects. Health care agents (appointed under DPAHC's) and next-of-kin or guardians must be given descriptions of both proposed research studies and the obligations of patients' representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interests.

c. **IRB Procedure.** The IRB shall make a determination in writing of each of the criteria listed in 9.12b. If these criteria are met, the IRB may approve the inclusion of incompetent subjects in research projects on the basis of informed consent from authorized representatives or next-of-kin as described in 9.12 a(1).

9.13 PAYMENT OF SUBJECTS

a. **Policy.** VA policy prohibits paying patients to participate in research when the research is an integral part of a patient's medical care and when it makes no special demands on the patient beyond those of medical care. Payment may be permitted, with prior approval of the IRB, in the following circumstances:

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(1) No direct subject benefit. When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated, non-VA institutions is to pay patients in this situation.

(2) Others being paid. In multi-institution studies, where patients at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed.

(3) Comparable situations. In other comparable situations in which, in the opinion of the IRB, payment of patient volunteers is appropriate.

b. Procedure. Prospective investigators who wish to pay research subjects shall indicate in their proposal the justification for such payment with reference to the criteria listed and, in addition, shall:

(1) Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject;

(2) State the terms of the subject participation agreement and the amount of payment in the informed consent form; and

(3) Substantiate that subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure on the veteran patient to volunteer for the research study.

c. Committees. R&D Committees and IRBs shall review all proposals involving the payment of subjects (in excess of reimbursement for travel) in the light of the policies in this chapter.

d. Research Offices. The research office shall ensure that IRB-approved payment to subjects is made from "medical and prosthetic research funds" (including General Post funds).

9.14 USE OF VA RECORDS FOR RESEARCH AND DEVELOPMENT

a. VA personnel are bound by all legal and ethical requirements to protect the rights of R&D subjects, including the confidentiality of information that can be identified with a person.

b. VA personnel may obtain and use for approved R&D purposes medical, technical, and administrative records from other VA facilities as well as those available locally. Requests for records from other facilities must be approved by the R&D Committee and the facility Director before being submitted to the appropriate R&D service director in VA Central Office.

c. Persons not employed by the VA can only be given access to medical and other VA records for R&D purposes within the legal restrictions imposed by such laws as the Privacy Act of 1974, and 38 U.S.C. Requests for such use must be submitted to the AsCMD/R&D (Associate Chief Medical Director for Research and Development) in VA Central Office at least 60 days before access is desired. Requests for information filed pursuant to the Freedom of Information Act ordinarily require a response within 10 working days. Agency implementing guidelines and policy must be adhered to when such requests are received so that a timely reply can be made.

9.15 INVESTIGATIONAL DRUGS IN RESEARCH WITH HUMAN SUBJECTS

a. The use of drugs in research must be carried out in a responsible manner.

(1) The use of controlled substances, such as narcotics and barbiturates, requires even more stringent monitoring.

(2) The storage and security procedures for drugs used in research shall follow all Federal rules, regulations, and laws regarding controls and safety that pertain in ordinary clinical situations. Such procedures apply as well to drugs used for animal studies in basic research.

b. An investigational drug for clinical use is one for which a sponsor has filed an IND (Investigational New Drug) application with, and which has been approved by, the FDA.

(1) The use of an investigational drug in clinical research must be conducted according to a protocol approved by the Subcommittee on Human Studies and the R&D Committee of the VA medical center.

(2) The principal investigator of an investigational drug study is responsible for securing the informed written consent of each patient subject on VA Form 10-1086 in compliance with the procedures described in paragraph 9.11. The original of the signed informed consent form, VA Form 10-1086, will be filed in the patient's medical record.

(3) A VA Form 10-9012, Investigational Drug Information Record, must be completed by the principal investigator and monitored by the R&D Committee.

(a) The original of this form will be kept on file in Pharmacy Service as a part of the study protocol.

(b) A copy for each patient, with the appropriate patient identification, will be filed in the patient's medical record.

(4) The principal investigator is also responsible for furnishing a copy of the approved protocol to the Chief, Pharmacy Service, of the VA medical center involved in the study.

c. When the Subcommittee on Human Studies and the R&D Committee approve the research study employing an investigational drug, VA Form 10-1223, Report of Subcommittee on Human Studies, will be prepared with copies forwarded to the investigator and to the Chief, Pharmacy Service. The original will be placed in the protocol file in the medical center's Research Office.

(1) The principal investigator will be responsible for obtaining the investigational drug from the manufacturer and delivering it or having it delivered, with proper identification, in accordance with FDA regulations (21 CFR 312) to the custody of the Chief, Pharmacy Service.

(2) The investigational drug will be ordered from Pharmacy Service on a properly completed VA Form 10-2577f, Prescription Form, signed by an authorized prescriber registered with the Chief, Pharmacy Service.

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d. The date contained in VA Form 10-9012 will serve as a protocol abstract and a copy of this form will be forwarded by Pharmacy Service for inclusion in the individual medical record each time a patient is entered in the study.

e. Prior to dispensing an investigational drug, Pharmacy Service will verify that an informed consent form, VA Form 10-1086, has been signed. Such verification shall be made by review of the consent form in the Pharmacy Service.

(1) The principal investigator must send Pharmacy Service a copy of this form for each patient entered in the study.

(2) Each time the drug is issued to laboratory personnel for use in laboratory studies, a written authorization signed by the principal investigator is required.

(3) The principal investigator must inform the Chief, Pharmacy Service, and the R&D Committee when a study involving investigational drugs has been terminated and must direct in writing the disposition of any remaining drug. M-2, part VII, "Pharmacy Service," was published for the compliance of all concerned; chapter 6 provides information on "Research and Investigational Drugs."

f. In the late stages of a drug's investigation, and in certain limited situations, the drug may be used as a humanitarian act outside the regular protocol in individual cases.

(1) In such cases, patients must become participants in the research protocol (21 CFR 50.3(g)) and an emergency life-threatening situation must necessitate the use of the drug (21 CFR 50.23(a)).

(2) Use of an investigational drug as a humanitarian act requires:

(a) Separate authorization from the Chief Medical Director for each patient outside the protocol (M-2, pt. 1, ch. 3, par. 3.03b);

(b) The filing of VA Form 10-9012 with the Chief, Pharmacy Service; and

(c) A report, to the facility Human Studies Subcommittee within 5 days (21 CFR 56.104(c)).

NOTE: Further details concerning such use of an investigational drug appear in M-2, part I, chapter 3.

g. In the case of a VA Cooperative Study employing investigational drugs, the Cooperative Studies Program Clinical Research Pharmacy at the VA Medical Center, Albuquerque, NM, will prepare the Investigational Drug Information Record which will list the name, address, and Social Security number of the study chairperson as it appears on VA Form 10-1436, Research and Development Information System Project Data Sheet.

(1) After the Investigational Drug Information Record has been signed by the Participating Investigator, one copy will be sent to the Chief, Pharmacy Service, of the Participating Investigator's VA medical center and one copy will be included in the protocol maintained in the medical center's Research Office.

(2) The Chief, Pharmacy Service, of the participating investigator's VA medical center will also receive a copy of FDA Form 1671, Investigational New Drug Application (IND), a copy of the IND letter from the FDA, and FDA Form 1572, Statement of the Investigator, for the respective participating investigator from the Cooperative Studies Program Clinical Research Pharmacy.

(3) A copy of the "Report of Subcommittee on Human Studies" indicating the approval of the study must also be forwarded from the local Research Office to the appropriate Cooperative Studies Program Coordinating Center assisting the study.

h. The Cooperative Studies Program Clinical Research Pharmacy will be responsible for obtaining the investigational drug and for distributing it to the Chief, Pharmacy Service, of each authorized participating VA medical center.

i. The Pharmacy Service of each participating VA medical center will maintain records on the investigational drug dispensed and will make arrangements in accordance with applicable VA and FDA regulations for disposition of the unused drug when its participation in the cooperative study is terminated.

j. When a new drug or device is considered investigational, the full range of side effects, adverse reactions, and complications associated with it are unknown. When an investigational new drug or device is to be used with human subjects, the manufacturer develops a detailed statement or investigational protocol of:

- (1) How the testing is to be accomplished;
- (2) What the human volunteer is to be told about the nature of the research;
- (2) Benefits from participation in the research;
- (3) The risks and complications which may arise from the research, and
- (4) What are the alternatives to participation.

k. Indemnification Agreements. Because, as with all research, there may be a risk of injury or adverse reaction, the manufacturer will sometimes offer to indemnify the VA medical center at which the testing is to be conducted and the VA investigator who conducts the testing in order to induce their cooperation and participation.

(1) The General Counsel's opinion is that the indemnification agreements that are commonly used in such situations usually do little more than restate the common law rule of indemnity. Rarely does the manufacturer's indemnification shield the investigator or participating VA medical center from liability or serve to act as an insurer.

(2) Without some compelling reason, the VA will not enter into these types of indemnification agreements.

(3) If there is a compelling reason, execution of the agreement requires the express approval of the General Counsel.

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(a) Such agreements and their supporting documents must be forwarded to the General Counsel's Office in VA Central Office for review and approval prior to their execution.

(b) Supporting documentation should include, but not be limited to:

1. Local VA Medical Center Research and Development Committee approval;
2. Human Studies Subcommittee approval;
3. The protocol which both bodies reviewed;
4. Data supplied by the manufacturer; and
5. Other materials necessary for the General Counsel to render a determination.

9.16 VA/FDA MEMORANDUM OF UNDERSTANDING

a. There is a Memorandum of Understanding between the VA and the FDA. It was negotiated in order to facilitate communication and encourage effective cooperation between the agencies in the area of clinical research with investigational new drugs, including biological and medical devices, and to accommodate FDA site visits to Human Studies Subcommittees at VA facilities.

b. In 1977, in response to a congressional directive, FDA developed a program to assure the quality of biological research data intended to support the approval of new drugs, biological, and medical devices. The main objectives of this program are to:

- (1) Assure protection of human subjects participating in the research;
- (2) Assess, through audit procedures, whether data submitted to FDA in specific studies are valid; and
- (3) Determine whether clinical investigators and Human Studies Subcommittees or IRBs (Institutional Review Boards) are complying with the regulations. *NOTE: FDA has applied the same standards of performance to Federal institutions and Government employees that it has applied to private industry.*

c. The following procedures have been adopted by VA and FDA:

(1) FDA will notify the medical center Director at the VA medical center whenever a clinical investigator or Human Studies Subcommittee IRB is to be inspected so that suitable arrangements for the inspection may be made.

(2) VA will facilitate access to administrative records and patient medical records associated with any investigational new drug and device research subject to FDA regulations and will also provide copies of those records upon the official request of an FDA investigator. Access to these records is authorized under the Privacy Act of 1974 (5 U.S.C. 552a(b)(3) and (7)) and the VA confidentiality statutes (38 U.S.C. 5701(b)(3), 5705(b)(1)(C), and 7332(b)(2)(B)).

(3) VA will review internal guidelines for clinical research with investigational new drugs and medical devices to assure that VA guidelines are consistent with FDA

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regulations for the conduct and reporting of investigational studies. Such review will also be conducted with regard to VA Human Studies Subcommittee IRB procedures.

(4) FDA will promptly advise the VA, through the liaison officer, of any violative findings resulting from investigations into the performance of clinical investigators or Human Studies Subcommittees IRBs associated with the VA.

(5) Following the inspection, FDA will forward to the VA liaison officer and the VA medical center Director a copy of any post-inspection correspondence to the clinical investigator or Human Studies Subcommittee IRB Chairperson resulting from the inspection. Upon request, FDA will send to the VA liaison officer copies of specific inspection reports and reviews pertaining to VA clinical investigators and Human Studies Subcommittees IRB inspections.

(6) In accordance with 21 CFR 20.85, VA agrees to maintain the confidentiality of any information from an FDA open investigatory file provided to VA under this agreement.

(7) FDA recognizes that disclosure of information obtained from VA records is subject to restrictions under the Privacy Act of 1974 and the VA confidentiality statutes. FDA personnel having access to drug, alcohol, and sickle cell anemia treatment records subject to the confidentiality provisions of 38 U.S.C. 7332 are not permitted to redisclose patient identities, directly or indirectly, in any manner in any report or audit documents which are created in accordance with this agreement. Violations of 38 U.S.C. 7332 may result in the imposition of fines and other adverse consequences.

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APPENDIX 9A**CATEGORIES OF EXEMPT RESEARCH**

Research activities in which the only involvement of human subjects will be in one or more of the following categories, are exempt from review by VA (Department of Veterans Affairs) Subcommittees on Human Studies and other IRB's (Institutional Review Board) used by VA investigators:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:
 - a. Research on regular and special education instructional strategies, or
 - b. Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement) survey procedures, interview procedures or observation or public behavior, unless:
 - a. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
 - b. Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior that is not exempt under paragraph 2, if:
 - a. The human subjects are elected or appointed public officials or candidates for public office, or
 - b. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:
 - a. Public benefit or service programs.
 - b. Procedures for obtaining benefits or services under those programs.
 - c. Possible changes in or alternatives to those programs or procedures.

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d. Possible changes in methods or levels or payment for benefits or services under those programs. *NOTE: This exemption was not originally intended for research conducted in a hospital setting. Although included in the exemption list, VA policy requires that prior approval of its use be approved by the Associate Chief Medical Director for Research and Development (12).*

6. Taste and food quality evaluation and consumer acceptance studies:

a. If wholesome foods without chemical additives are consumed, or

b. If a food is consumed that contains a food ingredient at or below the level of safety and for a use found to be safe, or agricultural chemical or environmental contaminant at or below a level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

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APPENDIX 9B

ACTIVITIES APPROPRIATE FOR EXPEDITED REVIEW

NOTE: *Research that requires any invasive procedure (with the exception of the procedures described in paragraph 4) is regarded as involving more than minimal risk and hence is not appropriate for expedited review.*

NOTE: *Expedited review may be used for minor changes in previously approved research during the period for which approval is authorized.*

Activities appropriate for expedited review are:

1. Collection of:

- a. Hair and nail clippings, in a nondisfiguring manner;
- b. Deciduous teeth; and
- c. Permanent teeth if patient care indicates a need for extraction.

2. Collection of excreta and external secretions including:

- a. Sweat;
- b. Uncannulated saliva;
- c. Placenta removed at delivery; and
- d. Amniotic fluid at the time of rupture of the membrane prior to or during labor.

3. Recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as:

- a. Weighing;
- b. Testing sensory acuity;
- c. Electrocardiography;
- d. Electroencephalography;
- e. Thermography;
- f. Detection of naturally occurring radioactivity;
- g. Diagnostic echography; and
- h. Electroretinography.

NOTE: *It does not include exposure to electromagnetic radiation outside the visible range (for example, X-rays, microwaves).*

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- 4. Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an 8-week period and no more than two times per week, from subjects 18 years of age or older and who are in good health and not pregnant.**
- 5. Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of teeth and the process is accomplished in accordance with accepted prophylactic techniques.**
- 6. Voice recordings made for research purposes such as investigations of speech defects.**
- 7. Moderate exercise by healthy volunteers.**
- 8. The study of existing:
 - a. Data;**
 - b. Documents;**
 - c. Records;**
 - d. Pathological specimens; or**
 - e. Diagnostic specimens.****
- 9. Research on individual or group behavior or characteristics of individuals, such as:
 - a. Studies on perception;**
 - b. Cognition;**
 - c. Game theory; or**
 - d. Test development, where the investigator does not manipulate subjects' behavior and the research will not involve stress to subjects.****
- 10. Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.**

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APPEND

PROCEDURES FOR OBTAINING INFORMED CONSENT

1. No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. NOTE: See paragraph 9.06 for exempt.

a. An investigator will seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence.

b. The information that is given to the subject or the representative will be in language understandable to the subject or the representative.

c. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

2. Basic elements for informed consent

a. Except as provided in subparagraphs 2c and 2d, in seeking informed consent the following information will be provided to each subject:

(1) A statement that the study involves research.

(2) An explanation of the purposes of the research and the expected duration of the subject's participation.

(3) A description of the procedures to be followed.

(4) Identification of any procedures which are experimental.

(5) A description of any reasonably foreseeable risks or discomforts to the subject.

(6) A description of any benefits to the subject or to others which may reasonably be expected from the research.

NOTE: An explanation will be provided as to whether compensation and/or medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained.

(7) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(8) A statement describing the extent, if any, to which confidentiality of information identifying the subject will be maintained.

(9) For research involving more than minimal risk, an explanation as to whether the research is justified in terms of the potential benefits to the subject and to others, and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

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(10) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(11) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(12) A statement that a veteran-subject will not be required to pay for treatment received as a subject in a VA research program. Investigators should note; however, that veterans in the "discretionary work load" category are subject to making a copayment if so indicated by a means test (M-1, pt. 1, ch. 4, par. 4.30). The veteran subject will receive medical care and treatment for injuries suffered as a result of participating in a VA research program, in accordance with Federal law.

b. Additional elements of informed consent. When appropriate, one or more of the following elements of information will also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research, consistent with the Federal laws concerning veterans' eligibility for medical care and treatment.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(7) A verbatim statement:

"I authorize the use of my bodily fluids, substances, or tissues.";

NOTE: Required if the researcher believes that bodily fluids, substances or tissues of a research subject could be part of or lead to the development of a commercially valuable product.

(8) A statement regarding any payment the subject is to receive.

(9) A verbatim statement:

"I have been informed that because this study involves articles regulated by the FDA (Food and Drug Administration), the FDA may choose to inspect research identifying me as a subject of this investigation." NOTE: Required if research involves a drug with an IND (Notice of Claimed Investigational Exemption for a New Drug) or a medical device with an IDE (Investigational Device Exemption).

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APPENDIX 9C

c. An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

- (a) Public benefit of service programs;
- (b) Procedures for obtaining benefits or services under those programs;
- (c) Possible changes in or alternatives to those programs or procedures; or
- (d) Possible changes in methods or levels of payment for benefits or services under those programs.

(2) The research could not practicably be carried out without the waiver or alteration.

d. An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

- (1) The research involves no more than minimal risk to the subjects;
- (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- (3) The research could not practicably be carried out without the waiver or alteration; and
- (4) Whenever appropriate, the subjects shall be provided with additional pertinent information after participation.

e. The informed consent requirements stated are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

f. Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law. (Approved by the Office of Management and Budget under Control Number 9999-0020.)

COOPERATIVE STUDIES PROGRAM

GUIDELINES

FOR THE PLANNING AND CONDUCT OF
COOPERATIVE STUDIES
OFFICE OF RESEARCH AND DEVELOPMENT
DEPARTMENT OF VETERANS AFFAIRS

September 1997

CSP
COOPERATIVE
STUDIES PROGRAM

OFFICE OF RESEARCH
AND DEVELOPMENT

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I. INTRODUCTION

The purpose of this manual is to describe practices and procedures for the organization and operation of Cooperative Studies Program (CSP) studies in the Veterans Health Administration (VHA). Cooperative studies are those in which investigators from two or more VA medical centers agree to study collectively a selected problem in a uniform manner, using a common protocol with central coordination.

Although cooperative studies are generally not appropriate for the early development and refinement of new therapeutic techniques, they are particularly advantageous in the later stages of evaluation of safety, efficacy and cost effectiveness of health care interventions that have already had the necessary preliminary trials in humans. Clinical trials and health services research studies of this type as well as some epidemiologic studies can benefit from a multicenter approach that facilitates the accumulation of patient samples that are:

- Sufficiently large to provide a definitive answer to the research questions. For medical conditions that are relatively rare, cooperative studies may be the only feasible approach, but even in more common conditions, knowledge can be accumulated more rapidly by pooling the observations made in several facilities.
- Sufficiently diverse to permit broad generalization of results.

The large number of medical centers within the VA presents an ideal environment for conducting multicenter cooperative studies. The VA has a large and relatively uniform patient base; this is especially appropriate for research that addresses medical problems and diseases prevalent in the veteran population. These characteristics facilitate the conduct of multicenter studies that require strict adherence to a common protocol. In this setting, it is more likely that the essential patient follow-up will be completed.

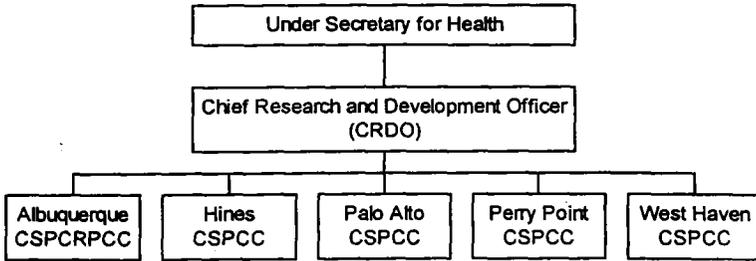
Successful cooperative studies require central administration to ensure uniformity of research methodology as well as fiscal control. The administrative structure of the VA contributes to this kind of coordination.

The Cooperative Studies Program, a division of the Department of Veterans Affairs Office of Research and Development, was established to provide coordination and support for multicenter research studies that fall within the purview of the VA. When appropriate, CSP works with other divisions of the VA to promote cooperative studies.

CSP has five coordinating centers (see figure 1): four statistical/administrative coordinating centers and one pharmacy coordinating center. The four Cooperative Studies Program Coordinating Centers (CSPCCs), located at the VA Medical Centers in Hines, IL, Palo Alto, CA, Perry Point, MD, and West Haven, CT, provide biostatistical and data processing assistance for CSP studies and also ensure their compliance with Cooperative Studies Program guidelines. There is a Human Rights Committee established at each Coordinating Center that reviews the ethical aspects of proposed studies.

The fifth center, unique to CSP, is the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC), affiliated with the VAMC in Albuquerque, NM. CSPCRPCC was established to provide additional resources for all CSP studies that involve drugs or devices. Personnel from this center help in the planning and development of the study, participate in monitoring the study, serve as liaison between the pharmaceutical industry or manufacturer and the CSP, provide guidance and information on Food and Drug Administration regulations, and centrally control and distribute study drugs and devices.

In a cooperative study, certain persons and groups have specific responsibilities. These *Guidelines* attempt to identify the most important tasks and responsibilities. A successful cooperative study requires communication, cooperation, and a willingness to pursue a common goal. We recommend that those interested in proposing a CSP study communicate with the CSP office in VA Headquarters if additional information is needed.

FIGURE 1. Organization of Cooperative Studies Program (CSP)

See Appendix A for names, addresses and FTS numbers relevant to the Cooperative Studies Program.

II. DEVELOPING A CSP STUDY

A. Submission and Review of Planning Request

A CSP study begins with the submission of a planning request by a VA investigator to the Chief Research and Development Officer (CRDO) in VA Headquarters. The investigator is designated as the Principal Proponent. A Co-Principal Proponent is named only when a clear and justifiable need exists; in general, the practice is discouraged. No more than two Principal Proponents may be named. A planning request should be no longer than 10 pages, and contain the following information:

- Objectives of the proposed research.
- Importance of the study topic to the VA and its patients.
- Justification of the need for a multi-site study and why it is feasible to conduct the study within the VA.
- Summary statement that the necessary preliminary research has been accomplished and that a large-scale evaluation should follow.
- Acknowledgment of VA policy to include women and minorities in clinical research.
- Description of the contemplated study design. Include the following items in the description as appropriate:
 - interventions/treatments/services to be compared
 - population to be studied
 - unit(s) of analysis
 - sampling strategy
 - type of data collection (retrospective or prospective)
 - randomization or observational approach
 - endpoints to be evaluated
 - logical links between questions, data, and endpoints
 - duration of the study
 - number of patients and participating medical centers

Other documents must accompany the planning request but are not included in the 10 page restriction:

- Statement of disclosure. A formal statement is required indicating that no financial or contractual relationship exists between the Principal Proponent and any organization involved in the trial that may constitute a real or apparent conflict of interest. If such a relationship or contract does exist, or appears to exist, full disclosure must be provided by the Principal Proponent. (See Appendix D.)
- Statement of eligibility. To be eligible for planning support, the Principal Proponent must either have, at minimum, a 5/8th's VA appointment or have applied for and received approval from the Eligibility Panel in VA Headquarters (Circular 10-88-95) within the previous nine months. In the latter case, a copy of the letter establishing eligibility to receive funds should be attached to the request.
- Cover letter from the Director and the ACOS for Research and Development at the Principal Proponent's Medical Center acknowledging and approving the submission.
- Curriculum Vitae (CV) of the Principal Proponent with address, telephone and fax number(s). (not to exceed 10 pages).

- Names, addresses, and telephone numbers of five to seven unbiased experts in the field who might be suitable to review the proposal. Planning requests will not be processed unless these names are included.

Seven copies of the request and CVs should be submitted.

A preliminary protocol outline and other relevant background materials including reprints and references may be appended to this request. However, only a portion of the submitted material may be distributed to the reviewers.

Investigators who have questions about submission of a planning request are encouraged to contact the CRDO. When it appears advantageous, the CRDO may suggest a consultation with the staff of one of the four CSPCCs. Similar support is available in the areas of cost effectiveness and decision analysis.

Planning requests are sent to four or more reviewers to evaluate the merit of the proposal. The decision to fund the study for planning will be made by the CRDO on the basis of the consultants' recommendations, together with other relevant considerations. Turnaround time for responses to planning requests is six to eight weeks unless additional information is requested from the Principal Proponent.

Although most CSP studies are supported by CSP funds appropriated by VHA, occasionally studies are funded from other VA sources or by outside sources such as the National Institutes of Health or the pharmaceutical industry. Regardless of funding support, all VA and CSP rules and regulations must be followed both in the development of the protocol and the conduct of the study unless specifically waived by the CRDO. If industry support is anticipated, industry representatives may be included in the planning process (see Section V.Q.).

B. Administrative Approval

A limited number of proposals may be evaluated and approved by the CRDO. Such proposals are defined by the length of the research - less than two years, and the budget - less than \$25,000. If approved, these proposals are assigned to a Coordinating Center and administratively reviewed midway through the course of the study. The planning and review process varies from that for a conventional CSP study in ways that are unique to each research plan.

C. Notification of Approval for Planning

When a study is funded for planning, the Principal Proponent is notified in writing by the CRDO, and informed as to which CSPCC the study will be assigned. The Director and the ACOS for Research and Development at the Principal Proponent's medical center are notified as well. The Chief of the CSPCC will identify the Study Biostatistician with whom the Principal Proponent will work. If the study involves drugs or devices, the Chief, CSPCRPCC will also be notified, and a Clinical Research Pharmacist (CRP) will be assigned to the study.

At the time a study is approved for planning, a TVX is distributed by Office of R&D, VA Headquarters inviting expressions of interest in participation. Interested investigators are encouraged to contact the Principal Proponent or the Study Biostatistician.

D. Planning a CSP Study: Participants

Planning and developing a CSP study requires close cooperation among several groups and individuals: the Principal Proponent, the CSPCC (represented primarily by the Study Biostatistician), the CSPCRPCC (represented primarily by the Study CRP), and the other members of the Planning Committee.

1. Principal Proponent

The Principal Proponent provides leadership in the planning process with support from CSPCC and CSPCRPCC personnel. Working closely with the Study Biostatistician, the Principal Proponent will:

- Nominate the members of the Planning Committee for approval by the CRDO and choose a date for the first planning meeting.
- Develop an agenda and distribute relevant material prior to the first meeting.
- Serve as Chairperson at meetings.
- Coordinate the writing of the protocol.
- Present and defend the protocol before the Cooperative Studies Evaluation Committee (CSEC).

2. Cooperative Studies Program Coordinating Center (CSPCC)

During the planning phase, the CSPCC, represented primarily by the Study Biostatistician, will:

- Help select members of the Planning Committee.
- Provide logistical support for the planning meetings, including identification of the meeting site, coordination of travel, and other related activities.
- Design the biostatistical and operational aspects of the protocol, including statistical and experimental design, definition of end points and data to be collected, data flow, sample size determinations, planned interval and final statistical analyses and data summaries, forms design and budget estimation.
- Arrange for review by the CSPCC Human Rights Committee.
- Arrange administrative support (e.g., typing, copying and distributing the proposal to members of the Planning Committee, and preparing and submitting the final document to CSPVA Headquarters for review by CSEC).

3. Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC)

For studies involving drugs, biologicals or investigational devices, the CSPCRPCC, represented primarily by the Study CRP, will:

- Assist in the development of the study design, particularly with regard to drugs, dosage regimens, packaging, and randomization and blinding strategies, pharmacokinetics and pharmacoeconomics.
- Assure compliance with drug or device accountability regulations and other legal requirements through the development of drug or device treatment and handling procedures.
- Act as liaison between the pharmaceutical industry or manufacturers and the Principal Proponent in the possible procurement of study drugs or devices, and develop a Letter of Agreement (LOA) with industry.
- Provide comprehensive drug information to study participants including pharmacological mechanisms, absorption, half-lives, steady-state levels, adverse reactions, interactions and similar items of interest in the formulation of drug studies.
- Prepare a Drug Information Report (DIR) for each primary study drug.
- Submit all DIRs to the CSPCC for review by the Human Rights Committee.

- Develop an adverse medical event reporting system for documenting and reporting routine and special adverse events, to assure FDA reporting guidelines are followed.

4. Planning Committee

The Planning Committee is responsible for preparing a final study protocol, which should reflect a collaborative, in-depth effort in its development with agreement on all major issues of the proposed study.

The Committee includes the Principal Proponent, the Study Biostatistician, the Study CRP (when appropriate), at least two potential participating investigators and VA or non-VA consultants. An expert in economic analyses will be included when this is an objective of the proposed study. If several disciplines are involved (e.g., medical and surgical), they should be reflected in the composition of the Committee. The total planning group consists of eight to ten people. Participation does not require VA affiliation. If industry support is planned, an industry representative may be invited to participate in the planning process.

E. Planning a Cooperative Study: The Process

The planning will usually require two meetings typically lasting two days each. Under special circumstances, additional planning activities may be funded.

The Principal Proponent submits a list of proposed attendees to the Chief, CSPCC as early as possible but no later than six weeks prior to a meeting. Clinical expertise other than the specialty of the Principal Proponent should be considered for representation on the Planning Committee. Requests for travel should be submitted to CSP/VA Headquarters at least four weeks prior to scheduled meetings.

The first planning meeting is held in Washington D.C. to facilitate the attendance of the CRDO. The final planning meeting is held in the vicinity of the CSPCC to permit attendance of other relevant CSPCC staff and to facilitate the review of the proposal by the Coordinating Center's Human Rights Committee. Meetings will not be funded unless all major participants are able to attend.

If the first planning meeting is not held within three months of the notification that planning is authorized, or if subsequent planning meetings and activities do not occur within six months of the first meeting, it will be assumed that the planning activity has ceased, and no further support for planning will be provided. It is the responsibility of the Chief, CSPCC to notify the CRDO to discontinue support for planning or, if the Chief, CSPCC concurs that the circumstances in a given situation are unusual and justify an exception from this practice, to petition the CRDO for an extension. Funding for the second meeting is contingent upon a satisfactory first meeting. After the first meeting, the Chief, CSPCC is required to reaffirm in writing to the CRDO that the study is viable and that planning activity should continue.

The CSPCC is responsible for sending the following materials to the Planning Committee prior to the first planning meeting. Relevant material should be submitted to the CRDO as well.

- CSP Guidelines.
- CSP Brochure.
- Planning Request - including relevant publications submitted by Principal Proponent.
- Reviews of the preliminary proposal.
- Detailed analysis of reviewers' comments by Principal Proponent and/or Study Biostatistician, including a point-by-point response to the reviewers' criticisms.

- A review of the literature to provide the Planning Committee with a basis for design decisions (e.g., effect sizes, estimates of variability, outcome measures).
- List of Committee members.
- Agenda.

At the first meeting, the Committee should consider and define:

- The primary question(s) to be answered by the study.
- Units of analysis.
- Secondary questions of importance. Secondary objectives, if any, should be restricted to a minimum.
- The population to be studied: inclusion/exclusion criteria. If women and/or minorities will be excluded, a compelling rationale for exclusion should be provided.
- The therapeutic regimen(s), if applicable.
- The variables to be measured and the outcomes of interest.
- Schedule and frequency of observations, laboratory tests and/or data collection.
- Comparisons of interventions/treatments/subgroups.
- Anticipated magnitude of differences in outcome measures to be detected.
- Logical links between questions, data, and endpoints.
- The number of patients needed and how they will be assigned to regimen groups. Patient accrual is often a problem in cooperative studies.
- Randomization procedures (if appropriate).
- Other specifics of the experimental design, (e.g., blinding techniques).
- Procedures to assure the scientific integrity of the study such as masking, independent endpoint assessment, quality assurance and audit procedures, and participating site performance standards.
- The methods of interval and final analyses to be employed.
- The need for core laboratories. These must be strongly justified.
- Preliminary estimates of budgetary support (personnel, travel, and "all other") needed for the Chairperson's office, participating medical centers and central laboratories (if any).
- The economic analysis component of the study, if relevant.
- Patient rights and informed consent issues.

If the Planning Committee decides that the study is not feasible, its clinical importance is questionable, or the study is untimely or irrelevant, this decision and the reasons for it will be communicated to the CRDO by the Chief, CSPCC. Otherwise, there should be some preliminary discussion of potential participating medical centers and specific planning for a formal determination of patient availability. This determination consists of prospective (preferred) or retrospective screening of actual patient intake by each of these

medical centers using the inclusion/exclusion criteria agreed upon. The review should be over a sufficient period of time to provide a reasonable estimate of the availability of study patients. This information should be available before the second planning meeting.

A plan for publications should be considered and incorporated in the planning process. Although it is early in the course of the study, it is recognized that publications are in fact the end product of a clinical trial (see Section VI.C. of these *Guidelines*). Therefore, it is the responsibility of the Principal Proponent, the Coordinating Center and the Planning Committee to anticipate that product. At the CSEC review, members will be instructed to pay particular attention to the publications plan.

Development of the protocol is a joint responsibility of the Planning Committee members. However, the primary responsibility lies with the Principal Proponent, the Study Biostatistician and the Study CRP.

The final planning meeting is spent refining the protocol and data collection forms, assessing preliminary patient availability estimates, formulating the final budget and conducting the Human Rights Committee review. (See Section III.A. for a description of the Human Rights Committee review.) To ensure that these goals are accomplished, and that there is a thorough human rights review, the Principal Proponent mails an essentially complete protocol including research data forms and informed consent documents to each member of the Planning Committee and the Human Rights Committee at least three weeks prior to the meeting. A preliminary budget (including justification of equipment or unusual items and brief but informative job descriptions) is also required by the CSPCC. The Principal Proponent must brief the HRC concerning material changes made at the final planning meeting. If submission of this material is late or if it is substantially incomplete, as determined by the Chief, CSPCC, the final planning meeting will be rescheduled. After the final planning meeting, the CSPCC will prepare the final proposal for submission to the Cooperative Studies Evaluation Committee, through CSP/VA Headquarters, by the required deadline.

If appropriate, the Study CRP begins negotiating with the pharmaceutical company early in planning to secure commitments for drug/device supplies for the study. The Principal Proponent usually makes the initial contact with the company, and the Study CRP follows up and completes the negotiations. The CRDO should be informed of all discussions. The Study CRP should attempt to secure a written commitment from each involved company during planning or at least prior to CSEC review. It is important that these negotiations be completed prior to CSEC review so that the start of the study will not be delayed once funding is approved. Industry representatives may participate in planning meetings, since they have detailed knowledge of the drugs involved (see Section V.Q.). If the Principal Proponent is negotiating with the drug company for securing funds in support of the study, the Chief, CSPCC should be involved in these discussions and if possible a letter indicating this support should be obtained prior to CSEC review.

The Biopharmaceutics/Pharmacokinetics Laboratory at the Albuquerque CSPCRPCC must be considered first when planning a laboratory component for the study. If the Principal Proponent determines that a core lab is required, the Chief, Biopharmaceutics/Pharmacokinetics Laboratory Section at the CSPCRPCC should be consulted. If this laboratory will be used in the study, the Chief should be included in the planning of the study, although not necessarily as a member of the Planning Committee.

F. Pilot Studies or Feasibility Trials

In some cases, it may be necessary to conduct a pilot study or feasibility trial before embarking on a full-scale study. Protocols for such pilot studies are generally developed through the usual planning process and presented to the CRDO who will determine if CSEC review is required. The completed pilot study may be reviewed by CSEC prior to the initiation of the full-scale trial.

G. Equipment-Intensive Studies

Studies that are equipment-intensive will be conducted in three phases:

- Install equipment in Study Chairperson's office. Evaluate equipment.

- Install equipment at two to three additional medical centers. Continue evaluation of equipment and monitor patient recruitment.
- Install equipment in all remaining centers.

H. The CSP Study Proposal

The objective of the planning meetings is to produce the final proposal. The CSPCC will be responsible for preparing the proposal for submission to CSP/VA Headquarters for CSEC review. To facilitate review, the proposal will be assembled in two volumes. The first volume contains the study protocol, study budget material, selected human rights documents and CVs of the Principal Proponent(s), Study Biostatistician, and any other members of the Planning Committee who will attend the CSEC meeting. When there is an economic analysis, the associated protocol, budget and CV are also included. All reviewers of the proposal are provided with this section. The second volume, containing a variety of supporting information, is provided to those individuals assigned as primary reviewers.

The following specifies the contents of each volume.

1. Volume I

- a. Table of Contents
- b. Letters of Submittal/Understanding

- 1) For an original submission:

If there are issues that should be called to the attention of CSEC, the CSPCC Chief will include them in the cover letter. The Chief will also comment on the appropriateness of the statistical analysis plan, take note of the budget, and address any budget issues that CSEC should consider. Similarly, the CSPCRPCC Chief will call the attention of CSEC to particular drug or device considerations that should be addressed during the review.

- 2) For a resubmission of a proposal:

If the proposal is a resubmission, the following documents are also required:

- CSEC Report: A copy of the CSEC report, which contains the recommendations made by CSEC at the time of the first review.
- Letter from the CRDO to the Principal Proponent that summarizes the results of the first CSEC review.
- A statement by the Principal Proponent or the Study Biostatistician that summarizes the specific changes made in response to CSEC recommendations, including a point-by-point response to each concern listed in the CSEC report and notification letter.

- c. Executive Summary/Abstract

The first page of the study protocol is a one-page abstract that succinctly states the research question(s) and the salient elements of the proposed study design including such information as the number of patients and participating sites, duration of patient intake and treatment (follow-up), definition of patient samples, treatment arms, and endpoints.

d. Study Protocol

To the extent possible and appropriate, the study protocol should be a concise description of proposed procedures, reserving detailed discussion of specialized technical procedures for inclusion as supporting information in the second volume. Since different types of studies will require different formats, the following is provided as a guide rather than an all-inclusive list of what is contained in the main protocol.

- Primary and secondary objectives. A clear description of the short and long-term objectives of the study should be provided, and the hypotheses to be tested specified.
- Background information and references indicating previous and current related research. If appropriate, reference to meta-analysis studies should be included. If the study involves the use of drugs, pertinent pharmacological and toxicological data should be summarized with appropriate documentation. This introductory section should also include a justification for the proposed research and an explanation of its significance to VA.
- Experimental design of the study, including controls.
- Flowchart of the basic study design.
- Patient recruitment, patient selection criteria and method of assignment of patients to comparative groups.
- Intervention/methods of treatment including, if appropriate, provision for double-blinding (and procedures for breaking the blind).
- Methods of follow-up and methods of assuring uniformity of intervention.
- Outcome measurements including specialized rating scales.
- Schedule of observations and laboratory tests; central readings and central laboratories.
- Statistical analysis section which describes how the major hypotheses or research questions will be tested, including the specification of major end points.
- Sample size issues including the assumptions used to determine number of patients required, duration of patient intake period, and number of participating medical centers. Other studies that could compete for patients should be noted.
- Quality assurance procedures.
- Plans for dissemination of study results, including manuscript preparation and writing.
- Plans for notifying patients of study results; plans for transition of patients from study treatment to regular care after their participation in the study ends.

e. Economic Analysis

The inclusion of an economic analysis in the proposal may be appropriate. Economic analysis has become an increasingly important issue as alternative therapies are compared.

When an economic analysis is included, the proposal should contain a separate section containing sufficient detail so that it can be evaluated by CSEC. As in the study protocol, the first page is a concise abstract of the proposed economic analysis study.

f. Human Rights Considerations

Before preparing this section, it is wise to review M-3, Part I, Chapter 9 which contains the agency position on these issues. This section should include:

1) Procedures and Ethical Issues

There should be a brief description of the procedures that will be used in the study to obtain the patient's voluntary consent to participate. This description specifies who can solicit consent, when consent can be solicited, and under what circumstances. It specifies whether there must be a witness present throughout the entire consent procedure or simply someone to witness the signature. The description can include details such as allowing the patient time to consider the issues or to consult others before giving consent, and permitting the patient to keep copies of the consent documents.

There should also be a comprehensive discussion of the ethical considerations that apply to the study. Related issues such as confidentiality of research data might also be included as part of the discussion. The Principal Proponent should identify all of the issues believed to be of importance from a human rights perspective. In discussing risks, there should be some indication of the degree of risk and a description of the safeguards to protect the patients. If surrogate or delayed consent is planned, this should be discussed and justified. The purpose of this discussion is to focus the attention of the Planning Committee on potential risks as well as to facilitate review by the Human Rights Committee, by CSEC and by the Subcommittee on Human Studies or the Institutional Review Board (IRB) at each of the participating medical centers.

One such issue that has both methodological and human rights implications is the CSP's responsibility for patients at the conclusion of their participation. In most treatment evaluations, particularly those that are double-blind, there should be consideration of the procedures that will be followed when a patient's participation in the study is completed, or terminated for other reasons. With some treatments, it may be necessary to break the code at this time in order to plan further treatment, and to inform the patient and/or the patient's physician. (See Section VI, "Concluding a CSP Study".)

2) Consent Documents

Study subjects indicate their willingness to participate in a CSP study by signing VA Form 10-1086, "Agreement to Participate in Research By or Under the Direction of the Department of Veterans Affairs". (See M-3, Part I, Chapter 9, Appendix 9C.) This document should describe the study in language that will be easily understood by the participant or his/her representatives so that a reasonable decision concerning participation can be made. It should include the following:

- A statement of the purpose of the investigation and a general statement as to its nature, i.e., how it relates to existing knowledge, what use may be made of the results obtained, and a description of any experimental procedures.
- Information describing the procedures to be used, including invasive techniques, restrictions on normal activities, long-term follow-up examinations, or the possibility of receiving inactive material ("placebo") in a double-blind trial.
- A statement of any known risks, inconveniences, or side effects that could be expected and the measures that will be taken to minimize hazard or discomfort and, where applicable, a statement that the risks cannot be predicted.
- A statement of any benefits that the subject may receive as a result of participation in the trial, including therapeutic benefits, payments, or recognition. (An

explanation will be provided as to whether compensation and medical treatment is available if physical injury occurs and, if so, the nature of the compensation or treatment, or where further information may be obtained).

- Information describing alternate courses of appropriate action, generally another accepted therapy, diagnostic procedure or health-related service, in lieu of participation in the study.
- A statement indicating that a decision not to participate in the study will not affect the subject's right to receive health care or any benefit to which he or she is entitled.
- When appropriate, a statement of the result to be anticipated if nothing is done, e.g., when neither an experimental nor a control drug is taken.
- An offer to answer any procedural inquiries.
- A statement that the subject may withdraw from participation at any time without prejudice.
- Signatures of the subject or guardian, person obtaining consent, and a witness.
- Date of signature.

The FDA further requires, for all projects that fall within its purview, that the following elements be included in the informed consent:

- An explanation of whom to contact for answers to pertinent questions about the study and patient's rights, and whom to contact in the event of a study-related injury to the patient.
- A statement that the provisions of the Privacy Act and Freedom of Information Act will be adhered to and that there is a possibility that the study's research records may be inspected and photocopied by the FDA.

When considered appropriate by the CSPCC Human Rights Committee, the following elements are also included:

- Circumstances under which the patient's participation may be terminated without regard to his/her consent.
- Any additional costs to the patient that may result from participation in the study.
- Consequences of a patient's decision to withdraw from the study and procedures for orderly termination of participation.
- A statement that any significant new findings developed during the course of the study that relate to his/her willingness to continue will be provided to the patient.
- An approximate number of patients involved in the study.

This consent form also may be used to ask the patient for permission to use Social Security or VA claim numbers for identification.

Each patient must be allowed to read (or have read to him/her) the informed consent form in order to have some understanding of the study before discussing it with the investigator. Each page of the document must be signed by the patient. In discussing the study with the patient, the investigator may provide additional details beyond those contained

in the consent forms, but no substantive addition, deletion, or modification to these statements is allowed. These sheets are the tangible evidence of what the investigator tells the patient. A copy is given to the patient when he or she signs the forms. If anesthesia, surgery, or other procedures are to be used, consent must also be obtained on an SF 522.

For policy regarding who may consent to the participation of incompetent patients in VA research, refer to VA Circular 10-90-052, Subject: Research with Surrogate Consent.

3) Human Rights Committee Report

This report provides a description of the Human Rights Committee discussions of the protocol during its review and lists any conditions for approval that the Committee may have stipulated. It must be signed by the CSPCC Human Rights Committee Chairperson.

g. Budget(s)

Every proposal contains a study budget including, when appropriate, beyond-core costs for CSPCC or CSPCRPCC, and/or a special laboratory budget. If the submission includes an economic analysis proposal, there should also be a budget for this component.

1) Study Budgets

The CSPCC will prepare the budget in the required format. Items to be included are the salaries of supporting personnel (including fringe benefits), consultation fees, equipment, supplies, investigational or study articles and other medications and chemicals, and costs of patient travel if required by the study. The budget should also note the FTEE required for the study. Supporting personnel are those hired solely for working on the study and are not existing personnel who work on the research as part of their regular duties. The Principal Proposer, with the assistance of the CSPCC, prepares position descriptions, including proposed grade levels, as part of the budget request. Positions should be filled at the grade level indicated in the study budget. Any exception must be justified. Personnel costs are increased 5% annually. Personnel hired for the study work solely for the study and are not to have other responsibilities unless they have completed their study functions. Salaries of Participating Investigators are supported by patient care funds rather than the CSP.

If needed by the study, VA and non-VA consultants and special research laboratories will be funded to provide expert advice, central readings and assessments, quality control and similar services. Funds to purchase equipment and supplies will be included only if the material will be used solely for the study. Patient travel is included only if the patient is required to travel for the sole purpose of being in the study. When medical services are furnished as part of an approved CSP study to a patient purely for the research program and not as part of approved medical care to an eligible veteran, it will be necessary to budget for these costs.

Although it is not VA policy to pay VA patients to participate in research when the research is an integral part of the patient's medical care, under some circumstances such payments are permissible (see M-3, Part 1, Chapter 9, 9.13, Payment of Subjects). If such payments are deemed appropriate by the Chief, CSPCC, they should be included in the budget.

Funding for extra travel and attendance at non-routine meetings before and during the study should be budgeted as a separate item. Travel needs such as extra training meetings and site visits are examples of non-routine travel (see Section V. for a discussion of routine study meetings).

Funds and FTEE provided for a CSP study are limited to the needs of the study and are not to be used to supplement other clinical or research activities. Furthermore, funds for a

CSP study at a given VA medical center are considered line item allocations for personnel, equipment, supplies and other operating costs and are not to be changed from one category to another without prior CSPCC approval. Transfer of funds from one CSP study to another at the same medical center requires prior CSP/VA Headquarters approval. Unexpended CSP funds and FTEE are not available locally for other research activities and shall be returned to CSP/VA Headquarters on a quarterly basis (or more frequently, at the discretion of the CSP), unless a specific exception is granted.

2) CSPCC Beyond-Core Budget

If the study requires additional costs beyond that of the center's core support, a separate beyond-core budget with justification will be prepared, and the totals will be included in the study budget.

3) CSPCRPCC Beyond-Core Budget

When applicable, cost estimates and justification for resources beyond core costs will be prepared, and these totals will also appear on the study budget.

4) Special Laboratory Budget

Central laboratories require strong justification. In general, CSP studies are not the appropriate environment for exploratory work.

If a special laboratory is needed for the study, a detailed budget estimate must be included, indicating costs of personnel, laboratory supplies, shipping and packaging of specimens and other necessary items. The totals will appear as a line item on the study budget.

5) Economic Analysis Budget

A detailed budget should follow the economic analysis protocol. The yearly totals appear as a line item in the study budget.

h. Curricula Vitae

This will be the final item in the first volume of the proposal. The curricula vitae (CV) of the Principal Proponent and the Study Biostatistician are required. If there is an economic analysis component, the CV of the person responsible for this part of the proposal should be included. Finally, if a consultant or other member of the Planning Committee will appear before CSEC, this CV should be included as well. Each CV should not exceed four pages. To remain within this limit, it may be necessary to include only those publications relevant to the study and indicate the additional number of publications.

2. Volume II – Supporting Information

Volume II contains a variety of information that is of special interest to the primary reviewers. The following sections should be included:

- Table of Contents.
- Biostatistical and Research Data Processing Procedures (BRDP).
- Research Data Forms.
- Drug Information Report (DIR).

- Drug Treatment and Handling Procedures (DTHP).
 - Tentative list of participating medical centers and a report of the patient availability survey.
 - Administrative issues, if any.
 - Other sections can be included as appropriate, e.g., description of training procedures, reliability studies, special laboratory procedures, definition of endpoints, central readings, etc.
- a. Biostatistical and Research Data Processing Procedures (BRDP)

This section contains plans for analysis that are as complete as can be envisioned for both periodic (monitoring summaries) and final analyses. It includes a statement of the variables to be analyzed and the intervals at which summaries and analyses will be done. The plan includes prototype tables, charts, data summaries, summaries of analyses, etc., and an outline of the format of the progress reports to be provided to the relevant committees. The anticipated final data summaries and biostatistical analyses are defined and described in detail. This section may also include a summary of: case report form completion and data flow; data quality monitoring procedures; and computing software/hardware to be used.

b. Research Data Forms

A complete set of essentially final research data forms is required when the proposal is submitted to CSEC for scientific evaluation.

Properly designed data forms are required for the collection of complete and accurate data in a clinical trial. The forms contain all information essential to the study. They should include only data that will be needed in the analysis; it is important to practice parsimony in developing data forms. Forms should be designed to ensure that data collected will be unbiased. They should also be easy for the researcher to use so that errors can be minimized. The forms should be formatted so that data can be efficiently entered into a computer for later retrieval and processing. Individual questions on the form should be constructed so that they are objective, single-dimensional and unambiguous. For these reasons, the data forms are designed jointly by the researchers including clinicians, the Study Biostatistician, Study CRP, and data processing personnel.

The order of the data forms and the elements in each form should be arranged to follow the sequence of the procedures required for conduct of the study. In addition to clear instructions for completion of the forms, self-explanatory codes and criteria should be available on the data forms for immediate reference.

Deficiencies in data forms can often be uncovered by a preliminary field trial so that revision can be made before the forms are distributed for use in all the participating sites. The CSPCC has responsibility for final approval of the data forms.

c. Drug Information Section

When the proposed study involves the use of drugs, the Study CRP develops a Drug Information Report (DIR) on each primary study drug. This report provides comprehensive information on the pharmacology, toxicology, and previous experience in the proposed indication. The report supplements the information presented in the background and rationale section of the protocol, and may be expanded by the Principal Proponent or other members of the Planning Committee. When determined appropriate, investigator brochures - prepared by pharmaceutical companies - may be included in the Drug Information Section in the Operations Manual and/or be distributed to investigators after the study begins.

d. **Drug Treatment and Handling Procedures (DTHP)**

A detailed procedure for handling drugs is written by the Study CRP in accordance with VA and FDA regulations. The DTHP includes detailed instructions for the receipt, distribution, administration and use, proper disposition and report requirements of the drugs or devices.

e. **Medical Center Participation and Patient Availability**

This section contains a list of medical centers that have expressed interest in participation in the study and describes the methodology and results of the assessment of patient availability.

f. **Other Supporting Information**

Additional sections can be included as appropriate. For example, if a central laboratory is needed, the protocol should include a detailed description of the procedures for obtaining specimens, evaluating results and transmitting data. Other material might include descriptions of training procedures, reliability studies, or definitions of endpoints.

i. **Submitting the Proposal**

All CSP proposals are submitted through the assigned CSPCC. After the final planning meeting and review by the CSPCC Human Rights Committee, the Principal Proponent sends the final version of the proposal to the CSPCC, where it is reviewed, typed in the required format and duplicated for submission to CSP/VA Headquarters. If the proposal is typed elsewhere, it should be provided on diskette to the CSPCC so that it can be reformatted according to CSP conventions.

CSEC meets twice each year in April and October. The associated deadlines for submission of completed proposals to the CSP/VA Headquarters for CSEC review are outlined in the following table:

PROPOSAL SUBMISSION DEADLINES		
CSEC Meeting	Deadlines for Submissions to:	
	CSPCC	CSP/VA Headquarters
April	Dec. 15	Feb. 1
October	June 15	Aug. 1

To allow sufficient time for review, typing, duplication, binding and distribution of the proposal, a complete final draft must reach the CSPCC at least six weeks before the deadline for submission to CSP/VA Headquarters. These deadlines must be observed or the review will be deferred to the next meeting. A protocol that is deficient in any important aspect will be returned to the Principal Proponent for appropriate action before it is resubmitted.

III. CSP REVIEW PROCEDURES

Ethical, scientific, professional, manuscript preparation and administrative aspects of the proposal are evaluated by the CSPCC Human Rights Committee (HRC), and the Cooperative Studies Evaluation Committee (CSEC). In addition, each proposal is reviewed prior to the CSEC meeting by at least three independent reviewers who provide written critiques. Finally, after CSEC scientific approval and CSP funding approval, the proposal is submitted for review by the R&D Committee and Subcommittee on Human Studies at each medical center being considered for inclusion in the study. If non-VA centers are participating, the proposal is submitted to the local Institutional Review Board (IRB) for review.

A. The CSPCC Human Rights Committee

Any study involving the use of human subjects requires consideration of the protection of the rights and welfare of the person volunteering to participate in the study. A Human Rights Committee (HRC) has been established at each CSPCC to provide these safeguards.

1. Composition

The Committee is composed of individuals from the community and VHA who have the interest and background required to consider the ethical and legal issues involved in the participation of human subjects in research. The Committee is chaired by a person who currently holds a VA appointment. At least two members are non-VA appointees who have no direct connection with research within a VA facility. At least one practicing physician from the community and one non-physician scientist will be on the Committee. Additional representation usually includes a member of the clergy, an attorney, a veteran and/or a member of a recognized minority group. Membership and procedures are consistent with appropriate sections of M-3, Part I.

2. Responsibilities

The responsibility of the HRC at the planning stage of the study is to determine if the protection of the patient's rights and welfare in the proposed study is adequate. Assessment is usually done at the final planning meeting but always prior to submission for CSEC review. The Committee must ensure that the patient (or guardian, if the patient is judged incompetent) will be fully informed of the meaning of and any risk in participation. This review should include an in-depth consideration of the protocol and the informed consent procedures and documents. If the study involves the use of a medical device, the HRC must make a determination (based on current FDA guidelines) as to the degree of risk inherent to the device.

The HRC may, on consideration of human rights issues only, accept the study as proposed, accept it with conditions, or reject it outright. If the study is rejected, the revised protocol must be approved by the HRC before it is submitted for CSEC review. A recommendation by a HRC may not be reversed except by its own action. Therefore, no study can be submitted to CSEC for evaluation until it has been approved by the HRC. If the study is accepted with conditions, the Study Biostatistician is responsible for ensuring that the conditions have been met before it is submitted for CSEC evaluation. A letter to this effect signed by the Chairperson, HRC is required.

The HRC provides a general assessment of the human rights aspects of the proposal. Neither this review nor the general assessment of feasibility, scientific merit, relevance and professional ethics by CSEC is a substitute for review by the local participating centers' R&D Committees and the Subcommittees on Human Studies or local IRBs.

B. Drug Information

When a study involves drugs, the Study CRP develops a Drug Information Report (DIR) on each primary study drug that provides comprehensive information including known side effects, adverse effects, contraindications and precautions. This report(s) is sent to the Chief, CSPCC who will distribute it to the Human Rights Committee, the Planning Committee and others as appropriate. A Drug Information Section containing all DIRs for a given study is incorporated into Volume II of the CSEC submission. This information is provided for use by CSEC, the PI's, and their R&D Committees and Subcommittees on Human Studies or their local IRBs.

C. Written Reviews for Cooperative Studies Evaluation Committee

Once CSP/VA Headquarters receives the proposal, it is reviewed to ensure that all the required information is included. Copies of the proposal are then sent to *ad hoc* reviewers who provide written critiques to the Cooperative Studies Evaluation Committee. These written critiques are available to the Principal Proponent, Study Biostatistician, and Study CRP prior to the meeting. The reviewers may request anonymity.

Reviewers are asked to comment on the importance of the project, its feasibility, the clarity and achievability of its objectives, the adequacy of the plan of investigation, the correctness of the technical details, the adequacy of safeguards for the welfare of the patients and any other pertinent features of the proposal. The biostatistical reviewer also is asked to comment on the character and definition of response variables, measurement, data collection, frequency of observations, sample size, plans for data processing and analysis and any other relevant features.

D. The Cooperative Studies Evaluation Committee

The Cooperative Studies Evaluation Committee (CSEC) reviews new and ongoing CSP studies and makes recommendations to the CRDO regarding the scientific merit of the studies.

1. Committee Members

Members of CSEC are appointed by the Secretary of the Department of Veterans Affairs upon recommendation by the CRDO. There are members representing many medical specialties as well as representatives from the FDA, the fields of epidemiology and biostatistics, and from health services research. All members have had extensive experience in clinical research and in the conduct of clinical trials. Members are appointed for a four-year term. Two members of CSEC, usually a biostatistician and a clinician, are assigned primary responsibility for reviewing each protocol. In addition, for new proposals, the Committee is augmented by an *ad hoc* member knowledgeable in the particular subject matter of the protocol being reviewed. The Chairperson of CSEC is nominated by the CRDO. The responsibilities of the Chairperson are to conduct the meeting and summarize the deliberations of the Committee. The CRDO and his staff serve as coordinators for the meetings. Appendix B lists CSEC members as of the publication date of these *Guidelines*.

2. The CSEC Review Process

The Principal Proponent and the Study Biostatistician appear before the Committee. If the proposal includes an economic analysis component, the consultant appears as well.

At the meeting, the Principal Proponent will be asked to make an opening statement not to exceed ten minutes, followed by a five minute statement from the Study Biostatistician. If there are Co-Proponents present, only one will make a formal statement. If there is an economic component, the individual responsible for preparing that protocol will also be expected to make a five minute statement. At the request of the Principal Proponent and with the concurrence of the CRDO, additional consultants may be available to answer questions and may make a five minute statement. These statements should be based on written documents that are distributed to CSEC members prior to the meeting.

They should provide a concise summary of the research problem and state why it should be supported by VA.

The Principal Proponent and the Study Biostatistician should take relevant notes at the meeting since in-depth reports of the CSEC proceedings are usually not provided.

After the formal statements, the *ad hoc* reviewer, the CSEC primary reviewers and the remaining CSEC members question the proponents on problems and issues they have identified. The proponents defend the protocol in an interactive discussion.

After the open session, the proponents are excused for the CSEC Executive Session. The *ad hoc* reviewer remains and participates as a voting member in this closed session, during which the Committee formulates recommendations.

3. CSEC Recommendations

Generally one of four actions is taken:

- Unconditional approval. The study is approved without changes and is recommended for funding.
- Conditional approval. The Committee approves the study with the understanding that the Principal Proponent and the Study Biostatistician will make certain changes or additions to the protocol. When the changes are made and are approved by the CRDO, the Chairperson of CSEC, and the CSEC primary reviewers, the study will be recommended for funding.
- Reject the study. The Principal Proponent will have an opportunity to review the CSEC report. If the Principal Proponent wants to resubmit the proposal to the CSP, a new request for planning must be sent to the CRDO.
- Reject or defer consideration of the study with recommendation for resubmittal. In unusual circumstances the Committee finds the study worthwhile, but in need of major revisions. In this case, should the investigator choose to submit a revised protocol, the CRDO may waive the requirement for an initial planning request and review.

The Principal Proponent(s), the CSPCC Chief, and the Study Biostatistician are informed of the CSEC recommendation immediately after the close of the Executive Session.

For new studies that are approved, CSEC assigns a numeric rating of the scientific merit of the proposal. Approval of a proposal by CSEC does not ensure funding. Action by this Committee constitutes a recommendation to the CRDO. Written notification by the CRDO constitutes the official action on the proposed study. Studies approved but not funded are reviewed on a continuing basis and will be dropped from the awaiting funding list if the CRDO determines that funding will not become available within 18 months after CSEC approval. If the Principal Proponent then chooses to resubmit a proposal, a new request for planning must be sent to the CRDO.

E. Review by Participating Medical Centers

When the Principal Proponent has been notified that funding is available, the CSPCC will then send the study protocol to the selected medical centers for their review. In order to avoid delay, the Participating Investigator (PI) should schedule the Research and Development (R&D) Committee and Subcommittee on Human Studies reviews (or, for non-VA centers, the Institutional Review Board [IRB] review) as soon as possible.

Comments, criticisms and/or suggestions for improvement of the proposal by the local R&D Committees are welcomed by the Cooperative Studies Program and will be seriously considered by study staff in preparing the Operations Manual (the primary procedural guideline for the study). Although some changes

may be made, all participating centers must conform to the final protocol requirements as well as the standard policies of the Cooperative Studies Program. In addition to the scientific aspects, the R&D Committee should address questions of feasibility. There must be an individual who is willing to serve as PI and who is eligible to receive research funding (i.e., at least 5/8 VA time or approved by the VA Headquarters Eligibility Committee). Usually, the PI will require active support from the PI's service and other services, e.g., Pharmacy, Clinical Laboratory. There may be a need for space. R&D Committee approval to participate implies that adequate staff, space, and other resources are available and that the medical center is willing to make a commitment to the study.

Recruitment of a sufficient number of patients is often a chronic problem in conducting cooperative studies. If the R&D Committee is aware of any circumstances that would seriously compromise the medical center's ability to contribute their quota of patients, these limitations should be taken into consideration in the review of the proposal (e.g., if there is another CSP study or a local study involving identical or very similar patients).

Although it is the preference of the CSP that a single standard consent form be used at all participating centers, the ultimate responsibility for the welfare of the patient resides at the individual center. The consent form document, developed by the Principal Proponent and approved by the CSPCC Human Rights Committee, should be considered as a prototype. If the Subcommittee on Human Studies from a participating medical center makes suggestions for changes, they will be seriously considered. Similarly, local variations can be incorporated into a standard document for use in all or most medical centers. When necessary and appropriate, variations across centers will be permitted with the approval of the Chief, CSPCC. Major changes must have the approval of the CSPCC Human Rights Committee.

Medical centers that approve participation in the study must submit a copy of the minutes indicating approval by their R&D Committee and Subcommittee on Human Studies or local IRB to the CSPCC as soon as they are available. VA Form 10-1223 should be used for reporting approval by the Subcommittee on Human Studies. If the study involves drugs/devices, a copy of these minutes must be sent to the Chief, CSPCRPCC by the CSPCC before any study agents can be distributed to the participating medical centers. A VA Form 10-9012 (Investigational Drug Information Record) must be completed and forwarded to the local Pharmacy Service by the PI prior to dispensing study drugs. Additionally, if the study is conducted under an IND, completion of VA Form 1572 (Statement of Investigator) will be required. In the case of an IDE, a signed agreement from the PI is required.

IV. INITIATING A CSP COOPERATIVE STUDY

A. Study Chairperson

Once a study is funded, the Principal Proponent is designated as the Study Chairperson. The Chairperson is responsible to the CRDO, through the Chief, CSPCC, for the conduct of the study. The appointment of a Co-Chairperson may be considered, e.g., when a study involves two major disciplines. However, there must be a clear and justifiable need, and the request for a Co-Chairperson must be approved by the CRDO. This decision is made most appropriately at the time of the initial planning meeting, but may occur after CSEC reviews the protocol. The Study Chairperson should not be a member of VA Headquarters staff, a current chairperson of a CSP study, nor function as the Study Biostatistician. It is not advisable to be concurrently Study Chairperson and PI of another CSP study. The Study Chairperson may not serve as the PI at his/her own facility.

There are a number of steps to be taken before patient intake can begin. These should be done in a timely fashion or there will be delay in funding and/or patient intake. These steps include:

- Revision of study protocol incorporating changes suggested by CSEC.
- Final selection of participating medical centers.
- Final review and approval of study data forms, and submission for OMB approval.
- Collaboration with CSPCC on development of an Operations Manual.
- Collaboration with CSPCRPCC on pharmaceutical and FDA issues.
- Nomination of members of the Executive Committee.
- Nomination of members of the Data Monitoring Board.
- Hiring support staff at the Chairperson's Office.
- Selection of core labs.
- Planning for acquisition of equipment and/or supplies.
- Planning of organizational meeting.
- Printing and distribution of the study data forms.
- Planning for study newsletter.

B. Selecting the Participating VA Medical Centers

Selection is based on indication of patient availability and other information. When the medical centers are identified, the Study Chairperson sends the list of nominations to the Chief, CSPCC. If there has been a significant delay (more than 12 months) between approval by the local R&D Committee and the Subcommittee on Human Studies and the initiation of the study for any reason (e.g., delay in release of funding, hiring freeze), it may be necessary for these committees to re-review the proposal or at least reaffirm their commitment to participate. In these instances, the CSPCC Human Rights Committee will also conduct a re-review.

When a medical center is informed that it has been chosen to participate, the PI, with the assistance of the ACOS/R&D, prepares a formal request for funds to the CRDO that is signed by the Medical Center

Director. This request duplicates the budgetary estimates provided by the CSPCC. Any deviation from the approved budget requires the endorsement of the Chief, CSPCC and the approval of the CRDO.

C. Forms Approval and Printing

Forms approval and printing are initiated soon after the CSPCC is advised that a study is likely to be funded. Although the forms were reviewed by CSEC, there should be another review before they are sent to VA Headquarters for approval. The Study Biostatistician will initiate this review with the Study Chairperson, the Study CRP, and relevant members of the CSPCC. The Study Chairperson may visit the CSPCC for the review. The Study Biostatistician prepares the request for VA and Office of Management and Budget (OMB) approval. If time permits, prospective Participating Investigators should be asked to review the forms prior to the approval and printing stage, since it becomes progressively more difficult to make changes later.

Some studies may use electronic forms in a distributed data entry system. In this case, the CSPCC will develop the system and provide the appropriate equipment and training to the participating centers.

D. The Study Operations Manual and Training Materials

After funding is approved, the Study Chairperson, Study Biostatistician, Study CRP, and other study members prepare an Operations Manual. This manual is used by the data collectors at each participating medical center and is intended to ensure that the study procedures are followed as uniformly as possible. It includes details of data collection, flow, recording and encoding, as well as procedures for reporting adverse medical events. A section on ethical conduct of the study should be included. In addition, the PI's responsibilities to the Pharmacy Service concerning prescription writing or drug ordering, the Pharmacy Service's responsibility to the PI and other items germane to the conduct of the study are clearly defined. If appropriate, the Operations Manual should also include instructions for using investigational or study supplies. The manual frequently consists of two volumes: Volume I is typed, assembled and distributed by the CSPCC; Volume II is typed, assembled and distributed by the CSPCRPCC. Other training materials may need to be prepared for the Organizational Meeting; e.g., videotapes or demonstrations.

E. Hiring and Training of Study Personnel

CSP study personnel are generally hired on term appointments. When an emergency situation arises concerning FTEE shortages or cuts, use of an IPA (through a non-profit organization or a service contract through the Acquisition & Materiel Management Service) will be used. The CSPCC needs to be fully informed of all IPA agreements. Approval authority for IPA agreements is delegated at the local VA medical facility level.

Training sessions for study personnel may take place before patient entry begins, usually at the time of the initial organizational meeting.

During the patient recruitment phase of the study, staffing will vary depending on estimated workload. Generally, many participating centers will employ full-time research assistants, though less than full-time may be sufficient. During follow-up, a part-time appointment is generally sufficient.

F. Investigational New Drug (IND) Application and Investigational Device Exemption (IDE)

The CSPCRPCC will determine if an IND or IDE is required and provide the necessary guidance regarding required FDA approvals and submissions. In most instances, the VA CSP is designated as the sponsor of the IND/IDE. In addition, the Study Chairperson and every investigator who will be participating in the study must be registered with the FDA and meet specific requirements. The CSPCRPCC will coordinate the preparation and submission of the IND or IDE in accordance with FDA requirements. The Study CRP will be the CSP representative to the FDA and will work closely with the Study Chairperson to resolve FDA-related issues and problems regarding the study. All correspondence with the FDA from study personnel is directed through the Study CRP.

The FDA will notify the sponsor in writing of the date they receive an IND or IDE application. Drug and significant risk device studies may begin 30 days after the FDA receives the application, unless the FDA notifies the sponsor to the contrary. Copies of FDA approved submissions must be on file at the CSPCRPCC before study articles can be distributed to participating medical centers. The CSPCRPCC will obtain a signed FDA Form 1572 (Statement of Investigator) or device agreement from the Study Chairperson and each PI as soon as the participating medical centers are selected. Drugs/devices cannot be shipped until the signed documents have been received by the CSPCRPCC. Routine updating of FDA Form 1572 will be coordinated on behalf of the sponsor by the CSPCRPCC at required intervals.

When a pharmaceutical company or device manufacturer acts as a sponsor of a study, the company accepts the responsibility for filing the IND or IDE with the FDA. In these cases, CSP requires a letter from the pharmaceutical company or manufacturer identifying their FDA assigned IND or IDE number. In such cases, a Letter of Understanding is also advisable to delineate all requirements of the CSP that are necessary to enable the company to meet its obligations as sponsor of the IND or IDE.

V. CONDUCTING A CSP STUDY

A. CSP Study Management and Monitoring

The CRDO delegates responsibility for each CSP study to the respective Chiefs, CSPCC who will in turn keep him fully informed and will forward to him those actions or recommendations that require his approval. Each study will be considered in a probationary status for the first year. Towards the end of this period, the Chief, CSPCC will provide a detailed report of progress to the CRDO with special attention to patient accrual and/or problems that might affect the successful completion of the study. The CRDO may discuss the contents of this report with the Study Chairperson and the Chief, CSPCC in writing or by telephone and recommend appropriate actions. Any study that does not reach at least 90% of the targeted accrual for the first year will be at risk for termination. The decision to continue a study is at the discretion of the CRDO.

Five groups share the responsibility for conducting and/or monitoring a CSP Study: the Study Group, the Executive Committee, the Data Monitoring Board, the CSPCC Human Rights Committee and the Cooperative Studies Evaluation Committee. The first three committees meet to review the operational and monitoring aspects of the study before patient intake begins. After patient intake begins, appropriate progress reports are distributed to these committees by the CSPCC at least three weeks before regularly scheduled meetings, and interim updates are provided between meetings. Studies lasting more than four years are reviewed by CSEC at three-year intervals or more often, should a specific need arise. Studies lasting four years or less are reviewed by CSEC at the halfway point of the study.

The standard schedule of meetings for the Study Group, Executive Committee and Data Monitoring Board consists of an initial meeting for organizational, informational and training purposes prior to patient intake, a meeting six to nine months after the initiation of patient intake, and annual meetings thereafter. After the first year, meetings will be scheduled as needed. In some cases, annual meetings may not be required, particularly during the follow-up phase. Ordinarily, meetings will not be held if the remaining period of patient follow-up is less than six months.

1. Study Group

The Study Group is chaired by the Study Chairperson and includes the Study Biostatistician, the Study CRP, all Participating Investigators and permanent consultants to the study. At the Organizational Meeting, the Study Biostatistician or Chief, CSPCC will make a presentation on research ethics and inform the group that site visits routinely take place. Two to three weeks prior to Study Group meetings, the Study Biostatistician prepares and distributes a report to the Study Group. At their meetings, the Study Group reviews the progress of the study, discusses any problems the investigators have encountered, and provides suggestions for improving the study. Results of blinded data related to study endpoints are not discussed with this group. When appropriate, the Research Assistant(s) from each center and other CSP personnel may also attend these meetings. It is the Study Chairperson's responsibility to write a report of each Study Group meeting within three weeks of the meeting, and send it to the Chief, CSPCC for distribution.

2. Executive Committee

The Executive Committee, chaired by the Study Chairperson, consists of four to eight members and includes the Study Chairperson, the Study Biostatistician, the Study CRP, the head(s) of any special central support unit(s) related to the study, two or three Participating Investigators, and selected consultants when necessary. If there are no more than five investigators, they may all be members of the Committee. This Committee acts as the management group and decision-making body for the operational aspects of the study. It decides on all proposed changes in the study and on any subprotocols or use of the study data, on publications of study results, and recommends actions on medical centers whose performance is unsatisfactory. As with the Study Group, the interim results of blinded portions of the study will not be presented to this group.

All major alterations in protocol design or operation of the study recommended by the Executive Committee are communicated to the CRDO for his approval and then submitted to the Data Monitoring Board for its written endorsement. The ACOS/R&D at each participating medical center is notified since major changes in the protocol may require resubmission to the local R&D and Human Rights Committees. If a significant-risk device is being evaluated, changes in the investigational plan must be instituted until they are approved by the CSPCC Human Rights Committee and a supplemental application is approved by the FDA. The Study Chairperson is responsible for writing a report three weeks of the meeting and sending it to the Chief, CSPCC for distribution.

3. Data Monitoring Board

The Data Monitoring Board (DMB) usually numbers six to eight members: experts in the subject matter of the study, two independent biostatisticians, and other appropriate technical or scientific specialists. Any study that involves patient intervention will have a DMB. When there is an economic analysis component, the Board will include an expert in health economics. The Study Chairperson, the Study Biostatistician are nonvoting study representatives and the CRDO and the Chief, CSPCC are nonvoting CSP representatives.

It is the responsibility of the Study Chairperson to nominate two members for each position on the Board to the Chief, CSPCC. The Study Biostatistician and/or the Chief, CSPCC usually will assist the Study Chairperson in selecting biostatistician nominations. Alternate nominations for any members may be suggested by the CRDO.

The Study Chairperson and the Study Biostatistician should not personally contact the nominees. The Chief, CSPCC will write or call those nominated to determine their willingness to serve on the Board and request a CV before forwarding the list to CSP/VA Headquarters. The CRDO will make final selection and issue a formal letter of appointment. A complete copy of the study protocol and a copy of the CSP Guidelines will be provided to each member by the Chief, CSPCC. The letter of appointment will extend through the last day of patient follow-up. If the services of Board members are required after that time, it will be on an *ad hoc* basis.

Data Monitoring Board members are highly qualified by background, training, experience, and knowledge in relevant disciplines and are responsible for monitoring, evaluating, and recommending on all aspects of the ongoing study. Members should be informed of CSP policy regarding conflict of interest. Conflict of interest may exist if a member has a substantial financial interest in an organization that could be significantly affected by the conduct or conclusion of the study; if the member serves as an officer of such an organization; or if the member has a consultancy or similar contractual relationship with such an organization. It is important to recognize that conflict of interest applies if these interests or relationships exist or appear to exist. A person who participated in the planning of the study or who is from the same institution as those playing key roles in the study should not be nominated. Persons from industry should not be nominated for studies involving the evaluations of industrial products of potential commercial value. It is the responsibility of the Chief, CSPCC to see that nominations put forth are in accordance with the spirit and intent of CSP policy. As is the case with Principal Proponents, DMB members should submit a statement of disclosure (see Appendix D).

The Data Monitoring Board provides a continuing critical and unbiased evaluation of the study progress and formulates operational policy consistent with the best current biomedical research practice. It does not initially evaluate the scientific merit or methodology of the study nor do its members subsequently participate in the study's conduct; these functions are performed by other committees. The Board maintains the confidentiality of interim results that are presented at scheduled meetings.

The major responsibilities of the Data Monitoring Board are:

- • • To consider the question of whether the study should continue. Inherent in this question are considerations such as patient accrual, overall study progress, treatment efficacy, and

effects, fullity, and proper monitoring and reporting by the CSPCC or other support units in the study.

- To assess the performance of each participating center and make appropriate recommendations regarding continuation, probationary status or termination.
- To review and provide recommendations regarding protocol changes and subprotocols.

As part of the study proposal, the Study Biostatistician prepares an outline of reporting procedures including prototype tables and graphs that will be used to present study data of various kinds (Appendix BRDP of the study protocol). The Data Monitoring Board is encouraged to provide a critical review of these proposed biostatistical monitoring procedures at their first meeting and to make recommendations or suggestions for improvement. At subsequent meetings, they may request new or different data displays. The Study Biostatistician prepares and distributes a report three weeks prior to meetings and at least one interim report between meetings. If data provided to the DMB are unblinded, tables containing these data will not be provided to the Study Chairperson, who must remain blinded. The Study Chairperson reviews the progress of the study and informs the Board of all proposed changes in the protocol, data collection forms or in plans for analyses. After a full discussion of all study issues, the Board can, if it wishes, meet in Executive Session (with the Study Biostatistician and CSP representatives) to formulate recommendations.

At their first meeting, the members of the Data Monitoring Board select a Chairperson with the assistance of the Chief, CSPCC. In addition to chairing each meeting, it will be this individual's responsibility to prepare a brief report of each meeting and send it to the Chief, CSPCC within three weeks. The report states those actions that the Board believes are necessary or highly desirable. These are phrased as recommendations to the CRDO. The DMB may also make suggestions that are not intended to be binding but are to be considered by the study representatives. When the report is received at the CSPCC, the Study Biostatistician will be asked to consult with the Study Chairperson and indicate how the recommendations will be implemented. The Chief, CSPCC will concur or add whatever comments he/she wishes, and forward the report to the CRDO with additional distribution to the Study Chairperson, the Data Monitoring Board and the Chief, CSPCC. After the meeting, the Study Biostatistician should telephone the CRDO's office and the Staff Assistant's office in order to make an informal report.

During the course of the study, the Study Chairperson and other members of the Study Group may not consult with DMB members without the approval of the Chief, CSPCC.

In regard to the question of liability, the decision of General Counsel was announced in a memorandum dated July 7, 1975. The Counsel stated that DMB members, when meeting on a study, are considered VA employees and, as such, are entitled to liability coverage under either 38 U.S.C. 4116 or the Doctrine of Official Immunity. This decision also covers the liability of non-VA members of the Executive Committee, the Human Rights Committee and the Study Group.

4. Human Rights Committee

In addition to reviewing the protocol for human rights issues prior to submission to CSEC, this Committee is responsible for ensuring that patients' rights and welfare are protected during the course of the study. At least once a year during the course of the study, the Human Rights Committee meets with the Data Monitoring Board to participate in that part of the meeting that deals with patients' rights and welfare. It is the responsibility of the Study Biostatistician and the Study Chairperson to provide the Committee with the appropriate information, including some or all of the data provided to the Data Monitoring Board and a summary of the progress of the study written in lay language. The Human Rights Committee Chairperson is responsible for writing a report of the meeting within three weeks of the meeting. This report should be sent to the Chief, CSPCC who will make the proper distribution. In rare instances where the HRC is blinded and the DMB is not (such as agreements between CSP and other agencies in interagency agreement funded studies), a member of the HRC, usually the HRC Chairperson, will be appointed to the DMB.

The local R&D Committees also should schedule an annual review by their Subcommittee on Human Rights and send a copy of the minutes of this review to the Chief, CSPCC. Each year, three site visits to participating medical centers are conducted by members of the CSPCC Human Rights Committee, accompanied by a member of the CSPCC. The purpose of these visits is to determine whether the human rights aspects of the studies are receiving proper attention. If possible, the Human Rights Committee member will observe at least one informed consent being given and will talk with study patients about their participation in that study. Upon returning from the site visit, the member will write a report of the visit and send it to the Chief, CSPCC. The report should not identify the patient by name. Since each CSPCC has more than three ongoing studies, a medical center in each study may not be visited each year. However, at least one Human Rights Committee site visit is made in connection with each study at some time during its ongoing phase.

B. Responsibilities In a CSP Study

The successful planning, organization, conduct, and conclusion of a CSP study requires the active cooperation of many individuals. Since participation in a VA CSP study is voluntary, all involved should have a clear understanding of their responsibilities and commitments. Agreement to participate implies a willingness to adhere to the research protocol in all respects. The approval for participation by the R&D Committee implies that it is feasible to conduct the study at that site, and that the medical center is prepared to provide the necessary and appropriate support. Involvement in a CSP study is demanding. A Study Chairperson and the Participating Investigators must be willing and able to devote time and energy to its success.

Participants should recognize from the outset of a CSP study that funding of an approved study will not be continued in the absence of objectively demonstrated satisfactory performance (e.g., number of patients enrolled, quality of data acquisition, etc.). The Study Chairperson and Study Biostatistician must monitor various aspects of performance closely throughout the study and routinely provide this information to the appropriate persons or groups. Personnel at participating sites must be notified if their performance is less than satisfactory. The Executive Committee must know that remedial action may be necessary and take such action promptly. The Data Monitoring Board must be prepared to make difficult decisions and recommendations, especially if poor performance appears to be placing the success of the study in jeopardy. In addition, the CRDO may decide to terminate the study if he determines that the study is not achieving its objective.

It is the responsibility of the CSPCC to inform patients if similar studies conducted by other agencies have been stopped prematurely, and the Data Monitoring Board has recommended continuation of the CSP study. In this situation, patients should be notified, by written communication, of the most recent information that has been made available to the public. Participating Investigators and study personnel at each participating medical center will be sent copies of the letter(s).

C. Meeting/Travel Arrangements

To initiate one of the regularly scheduled Study Group/Executive Committee meetings, the Study Chairperson should contact the Study Biostatistician at least six to eight weeks in advance of the proposed meeting date. However, as much as three to six months advance planning may be necessary to schedule hotel availability. The CSPCC Administrative Officer will select three sites with reasonable accommodations that minimize the cost of travel and per diem and which are convenient for travelers to reach, and calculate travel costs for each of them. If the cost projections for the three sites are comparable, the Study Chairperson may choose one. However, if the differences are significant, the site will be selected by the Chief, CSPCC. If the Study Chairperson wants to schedule a meeting at a more costly location, the attendees (excluding those from the CSPCC) must obtain the additional funds from sources other than locally or centrally directed VA research travel funds. Exceptions to these rules for selecting meeting sites will only be granted if there are unique and valid reasons to do so, such as availability of special laboratory facilities for training purposes. If plans are to have more than two participants per site attend or costs exceed original budget projections, special written approval of the CRDO is required. Committee members may be allowed to attend a national meeting in conjunction with a study meeting under the following conditions: the

CSP meeting must be scheduled immediately before or after the national meeting (not concurrent with); the national meeting must occur reasonably close to the regularly scheduled meeting time of the study; the CSP will not be responsible for extra per diem or fees associated with attending the national meeting; costs in excess of those projected for the selected site will need to be assumed by the participants.

When these details have been settled, the Study Biostatistician informs the Chief, CSPCC of the dates and place of the meeting, the names of the attendees and the addresses of any non-VA personnel who will be traveling on letters of agreement. An agenda indicating meeting times is attached. This letter, with appropriate justification, is forwarded to CSP/VA Headquarters as early as possible but no later than four weeks prior to the scheduled meeting date. Non-routine meetings of any of the groups necessitated by unusual problems arising during the study may be arranged on shorter notice by contact with the Chief, CSPCC.

The Data Monitoring Board generally meets in the vicinity of the CSPCC in order to facilitate the Human Rights Committee review. However, the initial meeting of the DMB may be held in Washington, D.C. if the CRDO is to attend.

Funding for travel to meetings of the Study Group, Executive Committee, Data Monitoring Board, and other authorized CSP study activities will be provided from CSP/VA Headquarters centrally directed travel funds. When the meeting has been approved, the CSPCC will notify all expected attendees and the associated ACOS offices and give them the necessary details. A scheduled meeting will be postponed if the expected attendance falls below 80% of those that are authorized to attend. Attendees should receive the agenda and any materials to be reviewed at the meeting at least three weeks prior to the scheduled meeting date.

It should be emphasized that all participants, including the Data Monitoring Board and CSPCC personnel, are dealing with privileged information and that confidentiality must be maintained.

D. Protocol Changes

Subsequent to CSEC approval, the Study Chairperson, Study Biostatistician, and Study CRP (if the study involves drugs or devices) may not unilaterally or collectively make study protocol changes without the appropriate approvals.

The Study Chairperson, Study Biostatistician, and Study CRP should discuss proposed study protocol changes among themselves before presenting such changes for approval. The Study Biostatistician and Study CRP must prepare an "Executive Summary of Proposed Study Protocol Change" form for their respective Centers that delineates the change, the need for the change, who the study's executive discussants were and the impact of the proposed change.

In all cases, the involved Center Chiefs (CSPCC and CSPCRPCC) and the CRDO must approve proposed study protocol changes. The CRDO will make the decision whether or not the proposed study protocol changes require the approval of CSEC. In cases of ongoing studies, proposed changes should be reviewed by the Executive Committee, and if approved, submitted to the CRDO for his review. After the CRDO's review, the proposal may be sent to the DMB. No substantial changes should be presented to the DMB prior to the CRDO's review. If the study is being conducted under an IND/IDE, protocol changes must be submitted to FDA prior to implementation.

E. Change in Funding Support

Changes in the study budget must be approved by the CRDO. Major changes may require another CSEC review. Requests for additional funding at participating centers must be initiated by the PI through the office of the ACOS/R&D at the center, with the appropriate justification and delineation of needs including personnel (FTE, GS grade, dollar costs), equipment and operating costs. This request should be forwarded to the CSPCC, with a copy to the Study Chairperson. If the Chief, CSPCC recommends approval and the CRDO concurs, the office of the ACOS/R&D of the participating medical center will be informed that an official request may be initiated through the Medical Center Director and the VISN Director.

Funds and FTE provided for a CSP study are limited to the needs of the study and are not to be used to supplement other clinical or research activities. Unused funds and FTE are to be returned to CSP/VA Headquarters on a quarterly basis.

F. Data Collection, Editing and Patient Entry Policy

Data are to be collected only on VA and OMB approved data forms supplied by the CSPCC or the CSPCRPCC. In general, data reported on the forms should be reviewed by the PI at each medical center before being sent to the CSPCC for biostatistical and data processing review and assessment. Data to be reviewed by individuals or groups other than those mentioned above (e.g., central readings of EEGs, EKGs, coronary arteriograms) are detailed in the study protocol. The protocol may also call for study data to be sent to the Study Chairperson for medical review. Some studies may utilize electronic forms and distributed data entry. In these cases, data is entered at the participating hospital and submitted to the CSPCC electronically. Review processes for such data will vary depending on individual study requirements.

It is against CSP policy for a patient to be enrolled simultaneously in two randomized clinical trials. It is also strongly urged that a patient enrolled in a VA CSP study not be enrolled simultaneously in another non-randomized study requiring informed consent. If an investigator wishes to do the latter, he/she must document in writing to the Chief, CSPCC why the patient's participation in the non-CSP study will not affect his/her participation in the CSP study. Screening forms in every CSP study should solicit information about other studies in which the patient might be participating. These issues should also be addressed at the Organizational Meeting of every CSP study.

All patients must sign an informed consent form. This form must be administered by the PI or his/her designee and signatures should be witnessed by a person unrelated to the study. A copy of each patient's signed informed consent document is sent to the CSPCC to verify that every patient has given consent. Original copies of VA Form 10-1086 are retained in the patient's official medical record (not research data records) at each participating medical center.

G. Breaking Study Blind

Most CSP studies involving drugs are double-blind studies in which neither the patient nor the PI knows which drug the patient is receiving. Emergency drug code envelopes are prepared by the CSPCC or CSPCRPCC and shipped with the study drugs to the Pharmacy Service of the participating medical center prior to the study starting. Each envelope is numbered with a unique patient randomization number and contains the treatment assignment for that patient. These envelopes are placed in the custody of the Pharmacy Service for the duration of the study. The blind (or treatment assignment) should only be broken if knowledge of the specific drug is essential to the medical management of the patient. In such an emergency, the Pharmacy Service may open the envelope and reveal the treatment assignment for a given patient to the PI. However, before doing so, the PI and the Pharmacy Service must comply with protocol procedures. Such procedures often include contacting the Study Chairperson or Study CRP before breaking the code.

The Pharmacy Service at the participating medical center must notify the Study CRP at the CSPCRPCC as soon as possible by telephone whenever a drug code envelope is opened. The emergency drug code envelope and its contents must be returned to the CSPCRPCC within 72 hours of the code break. Upon receipt of the code envelope, the CSPCRPCC will immediately inform the Study Biostatistician via telephone and send a copy of the envelope which is filed with the study documents at the CSPCC. When the study has been completed (or terminated early), the unopened envelopes must be returned to the CSPCRPCC. The CSPCRPCC will verify that the envelopes were or were not intact and notify the Study Biostatistician of their condition. Drug code envelopes should not be confused with the randomization code envelopes.

H. Subprotocols

Subprotocols to VA CSP studies are generally discouraged since they add burden to the participating clinic personnel, the CSPCC, the patients in the study, and to the Cooperative Studies Program costs. However, if a Study Chairperson or PI insist on proposing a subprotocol, the following steps are taken:

- 1) A formal protocol is written that includes background and justification, objectives, patient selection, informed consent documents, methods, data to be collected, sample size determination, and budget.
- 2) The subprotocol is reviewed and approved by a majority vote of the study's Executive Committee and Data Monitoring Board, and the CSPCC Human Rights Committee.
- 3) The subprotocol must be reviewed and approved by the R&D and Human Studies Committee at each anticipated participating center.
- 4) The committees reviewing the subprotocol determine if a patient's participation in the subprotocol will interfere with participation in the main CSP study. If it will, the subprotocol must be disapproved because the primary study must always take precedence.
- 5) If funding is required, non-CSP sources such as National Institutes of Health (NIH), the Agency for Health Care Policy and Research (AHCPR), VA Research Service's Merit Review Program, private foundations or pharmaceutical companies should first be contacted. Funding requests to CSP should be submitted only when other sources are not available. The Director of the MRS has agreed to review the subprotocols of investigators in CSP trials who want to perform Merit Review Studies related to the CSP trial. Review will be conducted even if the investigator has a separate Merit Review funded study.
- 6) All oversight committee approvals are conveyed to the CRDO as recommendations for action. Final approval must be obtained from the CRDO.
- 7) If the main protocol is conducted under IND/IDE, any subprotocol must be submitted to FDA prior to implementation.

All policies that govern CSP projects also apply to subprotocols. For example, manuscripts must be approved by the Executive Committee and the Chief, CSPCC.

I. Newsletter

Study newsletters are prepared and issued regularly by the Study Chairperson and/or Study Biostatistician. The newsletter is a primary means of keeping participants informed between meetings. The newsletter should contain items of general interest to the participants, progress and performance reports, drug-related issues, and discussion of any problems that arise. The newsletter should not include unblinded data or study results. Distribution will be made by the CSPCC.

J. Site Visits

Site visits by the Study Chairperson, the Study Biostatistician, the Study CRP, or other technical experts are not a routine part of CSP studies, but may be required in certain cases. When site visits are considered essential, they should be included as a special line item in the study budget. If an unforeseen problem arises that can be resolved only by visiting the medical center, a site visit may be funded if endorsed by the Chief, CSPCC, approved by the CRDO, and travel funds are available.

A site visit report should be sent within ten days to the Study Chairperson, who may simply endorse the report, add recommendations or conclusions, or, if necessary, attach a summary of the specific actions recommended by the Executive Committee to correct deficiencies that may have been discovered. The report is then mailed to the Chief, CSPCC for appropriate action.

On occasion, the FDA, as a part of their biomedical compliance monitoring program for sponsor, monitors, and clinical investigators, will visit a CSPCC or participating CSP facility. When the FDA announces their impending visit, the Study CRP is responsible for working closely with the Study Chairperson and the individuals being visited to prepare them for the FDA visit. Occasionally, collaborating pharmaceutical companies, whether sponsoring the IND/IDE or not, will wish to conduct site visits to assure compliance with FDA regulations. Such visits must be approved and coordinated by the CSPCC.

K. Replacement of a PI or Study Chairperson During the Course of a Study

CSP studies frequently take several years to complete. During that time, a PI or a Study Chairperson may find it impossible to continue with the study. Should this occur, suitable replacements should be found as quickly as possible in order to maintain the continuity of the study.

If a PI cannot conduct the study until its completion, he/she should give as much advance notice as possible to the Study Chairperson and, if possible, suggest an appropriate replacement. The Study Chairperson should then inform the Chief, CSPCC of the proposed change. If the study involves drugs or devices, the CSPCC Chief will inform the CSPCRPCC. The local ACOS/R&D should obtain endorsement of the center's R&D Committee for this change and inform the Chief, CSPCC, forwarding the R&D minutes when they are available. In cases of "emergency," with little or no advance notice, temporary assignment of an investigator by the local center is permissible until the formal replacement process is completed. If no suitable or available replacement for the departing PI exists, the center's participation in the study will be terminated. The CSPCC will notify the CSPCRPCC of all PI changes.

If the Study Chairperson cannot continue to direct the study, he/she should inform the Chief, CSPCC as early as possible so that nominations can be made to the CRDO. The nominee does not necessarily have to be from the same center as the original Chairperson. If the individual accepts the nomination, his/her medical center will be contacted to obtain the approval and support of the center and its R&D Committee. The local ACOS should initiate a letter endorsing the nominee as described previously. In cases of an "emergency," where there is little or no advance notice, the CRDO may temporarily appoint someone as Study Chairperson until the formal process is accomplished. However, if no suitable or available replacement Chairperson exists, the study may be terminated prematurely.

If an IND has been filed for the study, new PIs and/or new participating medical centers will be required to sign FDA Form 1572 for submission to the FDA. In the case of a significant risk device, addition of new participants may not be instituted until approved by the FDA.

L. Putting a Medical Center on Probation

If a participating center is not performing at the expected level, negotiations should take place between the Study Chairperson and the PI. If these discussions fail to correct the problem, the Executive Committee, with an endorsement from the Data Monitoring Board, can propose to place a participating site on probation. The proposal should be sent to the Chief, CSPCC for a decision. If the Chief, CSPCC concurs, the Study Chairperson should issue a probationary letter which states the reason(s) why the center was placed on probation and clearly specifies the criteria the PI must meet to be taken off probation in a specific time period. This letter should be sent to the PI through the CSPCC, which will forward the letter with a copy to the local ACOS/R&D and to the CSPCRPCC.

After the probationary period has elapsed, the Study Chairperson should issue a follow-up letter to the PI evaluating the performance during the period. The letter should clearly state that the site is either taken off probation for good performance or the PI has failed to meet the probationary requirements. In case of failure, steps may be taken to decrease support or drop the site from the study. In either case, a letter should be written to the Chief, CSPCC stating the rationale and the proposed action. The Chief, CSPCC will then seek the approval of the CRDO for the action.

In the event that the PI clearly acknowledges the lack of performance and even desires to be dropped from the study, the PI cannot act as an independent agent in the local decision. Instead, the PI should

contact the local ACOS/R&D or write to the Study Chairperson with a copy to the local ACOS/R&D acknowledging the performance and the desire to be dropped.

M. Early Termination of a Medical Center

During the course of a study, it is sometimes necessary to drop one or more medical centers from the study. Such action must have the prior approval of the CRDO. Early termination is usually based on recommendations from the Executive Committee and the Data Monitoring Board and most often reflects inadequate patient intake. This action will always be taken in response to what is considered the best interests of the study and does not necessarily imply poor performance on the part of the PI or the medical center. The recommendation should be sent to the Chief, CSPCC who will make comments and forward the recommendation to the CRDO for decision. If the CRDO concurs, he will inform the Chief, CSPCC, who will inform the ACOS/R&D of the medical center and the CSPCRPCC. After that contact, the Chief, CSPCC will write to the PI through the Director and the ACOS/R&D of the participating medical center. The letter will include the date of termination and information to the effect that funding not to exceed 45 days will be provided for the placement of study personnel. In unusual circumstances, a request for extension can be submitted to the CRDO. Funding for up to an additional 45 days (no more than 90 days total) may be provided if the need is documented and justified. In either case, accumulated annual leave must be included within the limits of salary support.

If equipment purchased for the study is needed at another medical center, the Chief, CSPCC will notify the ACOS/R&D at the terminated center that the equipment is to be transferred. If funds are not available for shipment, a request should be made to the Chief, CSPCC for such purpose. In the event that a new center is not yet identified, the Study Chairperson or Study Biostatistician may wish to have the equipment transferred to his/her center. In the event that the equipment is not needed by the CSP, it will be made available for other use.

Some medical centers are supported by a capitation plan instead of recurring salary and all other funds. If the medical center has not received equipment, medical devices, or supplies to be used for the study, then there would be no reason to terminate early. But, if the medical centers involved in a study have equipment, medical devices, or supplies that could be reallocated to a more promising center, then the center may be terminated early. In this case, the Executive Committee should set the criteria for terminating a capitation center. Once the criteria are established, the process would be the same as a center that receives recurring funds (see above).

N. CSEC Reviews of Ongoing Studies

All CSP studies are reviewed by CSEC at least once during their active phase. For studies lasting four years or less, this review will take place at the study's midpoint. For studies lasting more than four years, these reviews take place at three-year intervals. For these studies the first review is scheduled for the CSEC meeting nearest to the three-year anniversary of the first funding unless there has been an intervening CSEC review for another purpose. In the latter case, CSEC determines the date of the next review. Ordinarily, a three-year review will not be scheduled if fewer than 6 months remain until patient follow-up is ended.

Special reviews, e.g., requests for extensions of patient intake duration, are scheduled as required during the ongoing phase of the study. The Study Biostatistician and the Study Chairperson are responsible for scheduling these reviews through CSP/VA Headquarters. Submission deadlines are the same as for new proposals.

The CSPCC will be responsible for preparing the submission to CSP/VA Headquarters in the following format:

- Table of Contents.
- Executive Summary or Abstract of the study.

- **CSPCC Chief's Summary of Progress:** The Chief, CSPCC is required to conduct an in-depth review of the entire study and prepare an evaluative summary statement covering progress, performance and probability of successful conclusion of the study. He/she also presents a concise review of the budgetary aspects of the study.
- **Letters of Understanding (if necessary):** a letter from CSPCRPCC may be required to acknowledge requests for extension of patient intake or follow-up that affect supplies of drugs/devices.
- **Study Progress Report:** This section, jointly prepared by the Study Chairperson and the Study Biostatistician, includes a history of the study to date and a statement of current status. The latter includes the number of patients entered into the study (by time and medical center) and a comparison with the projected number; losses to the study, (such as dropouts and changes of therapy due to failure or toxicity) and a statement of when and why these occurred; comparison with study objectives; and estimates of the prospects of success. The report should include aggregated outcome data, and it should compare overall event rates with the rate predicted in the original protocol. At their discretion, CSEC may request outcome data by blinded treatment assignment, or, in unusual circumstances, unblinded outcome data. Reconsideration of the power/sample size issues may be necessary. In the case of a request for extension of patient intake or follow-up duration, this report should also contain a justification for the request. When investigators request an extension and/or an increase in budget, or if there is any problem with the conduct of the trial, the calculation of conditional probability must be provided to CSEC. In these cases, a letter from the Chair of the DMB should also be included in the mid-term report.
- **Previous CSEC Reports.**
- **Data Monitoring Board Reports or Minutes.**
- **Executive Committee Reports or Minutes.**
- **Human Rights Committee Minutes (including site visit reports).**
- **Bibliography of Study Publications.**
- **Budgets: The original budget approved by CSEC;** a budget showing actual costs to date; the difference between the two; and projected costs for the completion of the study.
- **Original study protocol and/or research data forms (only if significant modifications are being requested).**
- **Other supplemental material.**

O. CSP Study Files

Complete files are maintained on CSP studies at the CSPCC and CSPCRPCC and include copies of consent and data forms, protocols, committee reports, drug accountability data, and other documentation related to the review and conduct of the studies. The Study Chairperson, PI and laboratories should also maintain copies of all data forms and study related correspondence until the study is completed.

P. Periodic Reports

1. Research and Development Information System (RDIS)

The Office of Research and Development requires certain information annually from every VA medical center that conducts research (M-3, Part I, Chapter 4). The local R&D office at each medical center is responsible for compiling this information and will initiate the reporting process and provide current instructions. Each Study Chairperson and PI will be asked to provide information. Questions about reporting are best directed to the local R&D office.

Within 15 working days after the funding of the Study Chairperson's office in a CSP study, the Study Chairperson should complete a Project Data Sheet (VA Form 10-1436). This form will be completed annually during the course of the study and at termination. Complete instructions can be found in M-3, Part I, and the local R&D office can provide necessary assistance. Project Data Sheets must be reviewed for confidential data and thus should be submitted through the appropriate CSPCC with a copy to the ACOS/R&D. If the Study Chairperson has not previously been reported in the RDIS data base, a VA Form 10-5368 should also be completed and sent to the Biomedical Engineering and Computing Center (BECC) at Sepulveda.

2. Annual Progress Report to FDA

The sponsor of an IND/IDE is required to submit an Annual Progress Report to the FDA; the CSPCRPCC will coordinate this activity on behalf of the sponsor.

Q. Collaboration with Industry

The following are general guidelines that should be followed in collaborations with industry:

- VA and industry should establish the concept of mutual but not identical interests and distinguish principles from practice.
- Industry funds must be contributed to an independent foundation, and funds must be under the control of CSP - not industry or investigator.
- Industry may participate in planning meetings, Study Group meetings, Executive Committee meetings and Publication Committee meetings.
- Industry cannot participate in Data Monitoring Board meetings.
- Industry cannot have access to unblinded data prior to the end of patient follow-up.
- Industry should receive courtesy pre-publication manuscript for comments and receive acknowledgment for funding.
- Industry should not have any veto over publication.
- Funding from industry should be acknowledged in study publications.
- Industry should not release pre-publication data in any form.
- CSP should help in FDA preparations and be reimbursed for extra effort.

Detailed information regarding collaborative agreements with industry can be found in the document "Understanding the Contracting Practices in VA Cooperative Studies Program".

VI. CONCLUDING A CSP STUDY

A. Closing Down

In some instances, patients will still require treatment after their participation in a CSP study. The patient's treating physician should plan the transition from study treatment to whatever continued treatment is appropriate. If a patient has done well on a drug that is still investigational and the physician would like to continue its use, FDA regulations must be observed and a new source of the drug found. Final results of the study will ordinarily not be immediately available for the physician's guidance. When the final results do become available upon publication of the major manuscript, letters reporting the study results should be sent to all study patients. These should describe the results in lay language, and must be reviewed by the Human Rights Committee. Specific plans for handling the closeout phase, unblinding, and notifying investigators and patients of study results should be included in the original protocol (see Section II.H.1.d.).

When follow-up on all patients enrolled in the study has ended, the CSPCC has the responsibility for final data summaries and analyses of the study, which should be completed within a reasonable time after receipt of the last data forms at the CSPCC. The Executive Committee is responsible for the publication of all data and results of the study. Six months prior to the end of the study, the Executive Committee should submit a publication plan to the Chief, CSPCC, who will forward it to CSP/VA Headquarters. Material for publication should ordinarily be submitted within one year of receipt of all data at the CSPCC. Normally the Executive Committee will be funded for one meeting during this year to prepare the manuscript(s) for final publication.

At the close of the study the CSPCC should have physical possession of all study data. The CSPCC will maintain readily accessible files on the study for five years after its completion, at which time the data can be placed into storage and re-evaluated at five-year intervals regarding its continued retention. CSPCRPCC will maintain files for a minimum of five years after completion of the study. Participating medical centers can, at their discretion, discard files two years after the study is completed. However, local policies may require a longer period.

The CSPCRPCC, in cooperation with the Study Chairperson, the Study Biostatistician and the participating medical centers, will direct the return of all surplus drugs or investigational devices that were centrally distributed. The CSPCRPCC will provide a final accounting of drugs utilized by participants. The surplus drugs will be disposed of in a manner determined by the CSPCRPCC.

The sponsor of an IND/IDE is required to submit a Termination Report to the FDA shortly after completion of the study. The CSPCRPCC will coordinate this activity on behalf of the sponsor.

At the completion of the study, the CSPCC Administrative Officer will call the other coordinating centers to determine if equipment purchased specifically for the study can be usefully deployed to other studies and if so, will arrange for its transfer through the appropriate Acquisition & Materiel Management Service. Otherwise, such equipment will be disposed of in accordance with the regulations of the Regional Research Equipment Program (RREP) (Reference: VA Manual MP-2, Subchapter H, page 43.3-4, dated May 23, 1988).

Subsequent to final analysis, if data are used for meta analysis, the CSPCC Chief should be informed. Questions of appropriate use of CSP data will be referred to the CRDO.

B. Final Study Meeting

The Study Group and the Data Monitoring Board will have a final meeting as soon as the major analyses and results of the study are available for distribution and discussion. This meeting usually takes place after the manuscript writing meeting of the Executive Committee or its designated writing subcommittee(s). At this meeting, the Study Chairperson and the Executive Committee present the major study results and their interpretation to the PIs. The Study Group's discussion of the results may provide the manuscript writers with other useful interpretations and provide a forum for discussion among the PIs.

C. Publications

As stated earlier in these *Guidelines* (Section II.E.), the importance of publications cannot be overestimated. CSP considers the publication and dissemination of study findings to be of utmost importance.

Publications are to be made in a timely fashion. In collaboration with the Study Chairperson and Study Biostatistician, the Chief, CSPCC will establish a date for submission of the major manuscript. This date will usually be six months after funding for the last study personnel has terminated. If the major manuscript is not submitted on time, the Chief, CSPCC may request that the CRDO designate other study participants to write the manuscript.

The presentation or publication of any or all data collected by PIs is under the direct control of the study's Executive Committee. This is true whether the publication or presentation presents the results of the principal undertaking or the results of an ancillary analysis. The Chief, CSPCC must approve a manuscript prior to submission.

All publications must give proper recognition to DVA, VHA and CSP support. If an investigator's major salary support and/or commitment is from the VA, it is obligatory to list the VA as the primary institutional affiliation. Submission of manuscripts must follow the usual VA policy. Ideally, a subtitle is used stating, "A VA Cooperative Study," or, for example, in the case of shared funding, "A VA-NHLBI Cooperative Study." An alternative method is to list the study group as the final author, e.g. "The Veterans Affairs Cooperative Study Group on (study topic)". A footnote or acknowledgment should state: "Supported by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development" or "Supported by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development and the NHLBI by interagency agreement NO. XXX." CSPCC Chiefs are required to ensure that this policy is carried out for all study publications.

When a major manuscript has been submitted, a copy of the manuscript should be sent to CSP/VA Headquarters. When any manuscript is accepted for publication, the Study Chairperson and the Study Biostatistician should write a summary of the results and send it (along with a copy of the revised manuscript) to CSP/VA Headquarters. This summary should be a brief statement, no longer than a page, in direct and informal language, describing the results of the study and its importance. When the date of publication and the journal is known, that information should be sent to CSP/VA Headquarters. After CSP/VA Headquarters has received and approved the summary, it should be forwarded to the Office of Research Communications. CSP/VA Headquarters will work with the appropriate offices to coordinate publicity efforts for major publications.

A copy of the abstract from the published paper (including the complete journal reference and a brief lay-language summary of the study and the paper), should be sent to the Perry Point CSPCC for inclusion in the next *Cooperative Studies Update*. If the published paper does not include an abstract, the Study Chairperson or Study Biostatistician should write one. When reprints are available, the Study Chairperson should send 12 copies to the Chief, CSPCC. Two of these will be forwarded to CSP/VA Headquarters and a courtesy copy will be sent to other CSPCCs and the CSPCRPCC.

D. Administrative Repercussions

The CSP policies for data analysis and publications of results apply to all members of the study team (Study Chairperson, PIs, Study Biostatistician, etc.). If a Study Chairperson or site Principal Investigator has been discovered to be misusing study data or has submitted unauthorized manuscripts for publication, the following administrative actions may be taken (at the discretion of the CRDO):

- Removal as investigator
- Forfeiture of research funding
- Prohibition from receiving VA research funding for one to five years, commensurate with the seriousness of the infraction (at the discretion of the CRDO).

VII. CONCLUSION

The planning, review, initiation and completion of a CSP study is a complex process requiring close communication among all participants. We have prepared this document as a guideline, but we recognize the need for flexibility in the conduct of Cooperative Studies. We welcome suggestions from study participants for inclusion in subsequent editions of these guidelines.

APPENDIX A - CSP ADDRESSES

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APPENDIX B - COOPERATIVE STUDIES EVALUATION COMMITTEE

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*Members as of September, 1997

**Member serves through this date

APPENDIX C - GLOSSARY OF ABBREVIATIONS

ACOS	Associate Chief of Staff
AHCPR	Agency for Health Care Policy and Research
AMM	Acquisition and Material Management Service
BECC	Biomedical Engineering and Computing Center
BPLS	Biopharmaceutics/Pharmacokinetics Laboratory Section
BRDP	Biostatistical and Research Data Processing Procedure
CRDO	Chief Research and Development Officer
CRP	Clinical Research Pharmacist
CSEC	Cooperative Studies Evaluation Committee
CSP	Cooperative Studies Program
CSPCC	Cooperative Studies Program Coordinating Center
CSPCRPCC	Cooperative Studies Program Clinical Research Pharmacy Coordinating Center
CV	Curriculum Vitae
DIR	Drug Information Report
DTHP	Drug Treatment and Handling Procedures
DMB	Data Monitoring Board
DVA	Department of Veterans Affairs
EEG	Electroencephalogram
EKG	Electrocardiogram
FDA	Food & Drug Administration
FTE	Full Time Equivalent
FTEE	Full Time Equivalent Employee
FTS	Federal Telecommunications System
GS	General Schedule
HRC	Human Rights Committee
HSR&D	Health Services Research and Development
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IPA	Intergovernmental Personnel Act
IRB	Institutional Review Board
LOA	Letter of Agreement
MRS	Medical Research Service
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
OMB	Office of Management and Budget
PI	Participating Investigator
R&D	Research and Development
RDIS	Research and Development Information System
RR&D	Rehabilitation Research and Development
RREP	Regional Research Equipment Program
VA	Veterans Affairs
VAMC	Veterans Affairs Medical Center
VHA	Veterans Health Administration

**APPENDIX D - STATEMENT OF DISCLOSURE
STATEMENT FOR THE PRINCIPAL PROPONENT, THOSE SERVING IN AN AD HOC REVIEW OR
ADVISORY CAPACITY, AND MEMBERS OF DATA MONITORING BOARDS**

CSP # _____
(name of study)

Except as noted below, I am not an employee (part or full-time, paid or unpaid) of any organization(s) either involved in the study(s) under review or whose products or services would be clearly and directly affected in a major way by the outcome of the study(s), nor am I an officer, member, owner, trustee, director, expert, advisor or consultant of such an organization. It is important to recognize that conflict of interest applies if these interests or relationships exist or give the appearance of existing.

Except as noted below, I do not have any financial interest in any organization meeting the above criteria, nor does my spouse, minor child, nor an organization with which I am connected.
(State "None" or Identify any exceptions)

I will notify the Chief of the CSPCC promptly if (a) a change occurs in any of the above during the tenure of my responsibilities or (b) if I discover that an organization with which I have a relationship meets the criteria.

I am aware of my responsibilities for the maintenance of confidentiality of any non-public information that I receive or become aware of through this activity and for the avoidance of using any such information for my personal benefit or for the benefit of my associates or of an organization with which I am connected or with which I have a financial involvement.

Signature

Date

