OVERSIGHT OF NIH AND FDA: BIOETHICS AND THE ADEQUACY OF INFORMED CONSENT

HEARING

BEFORE THE

SUBCOMMITTEE ON HUMAN RESOURCES

OF THE

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT HOUSE OF REPRESENTATIVES

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CONTENTS

OVERSIGHT OF NIH AND FDA: BIOETHICS AND THE ADEQUACY OF INFORMED CONSENT

THURSDAY, MAY 8, 1997

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HUMAN RESOURCES,
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT,
Washington, DC.

The subcommittee met, pursuant to notice, at 10:05 a.m., in room 2247, Rayburn House Office Building, Hon. Christopher Shays (chairman of the subcommittee) presiding.

Present: Representatives Shays, Snowbarger, Pappas, Towns, and Kucinich.

Staff present: Lawrence J. Halloran, staff director and counsel; Anne Marie Finley, professional staff member; R. Jared Carpenter, clerk; and Cherri Branson, minority counsel.

Mr. SHAYS. I call this hearing to order. Next week the President will formally apologize to the survivors of the 40-year Tuskegee experiment, a federally funded study in which black men were allowed to suffer and die of a curable disease—syphilis—in the name of scientific research. Last week, this subcommittee heard testimony from Gulf war veterans ordered to take a potentially toxic drug for an experimental use without being informed of any possible side effects.

The road from Tuskegee to Baghdad is lined with other landmarks of scientific arrogance and human tragedy. Thalidomide, radiation experiments, the EZ measles vaccine trials—those notorious lapses in the protection of human research subjects and the complex ethical implications of emerging biomedical issues like cloning, gene therapies, and AIDS vaccine trials compel us to ask: How effective are current mechanisms to review ethical issues and detect violations of informed consent requirements?

What needs to be done so patient protections keep pace with scientific advances? Do we need a permanent national panel to serve as the arbiter of biomedical ethics issues? Physicians have a moral duty to inform human research subjects of the foreseeable risks of participation, and a duty to minimize those risks. The discipline of bioethics has evolved from the Hippocratic oath to the Nuremberg Code to current national and international standards to protect the health and human dignity of all who submit themselves to help advance scientific knowledge.

But the current system of bioethics review appears to be showing signs of age and disrepair. Multiple layers of review and enforcement provide a false sense of security that difficult issues are being confronted. The regulatory scheme lacks specific provisions to pro-

tect mentally ill, drug addicted and cognitively impaired persons involved in biomedical research. Local institutional review boards—the IRBs—considered the cornerstone of the entire bioethics review structure, are often hard-pressed to monitor research protocols and informed consent procedures on an ongoing basis.

By one recent estimate, more than half the federally funded research projects inspected by the FDA between 1977 and 1995 failed in some way to inform research subjects fully of the experimental nature of the medical procedure. Multi-site research studies further challenge the capacity of local IRBs to control the research nominally under their purview. The National Institutes of Health—NIH—are charged with the potentially conflicting duties to fund research, conduct research, and enforce bioethics regulations. As a result, the NIH Office of Protection for Research Risks—the OPRR—faces both institutional barriers and logistic obstacles in attempting to police thousands of research projects.

The third leg of what is supposed to be the national bioethics triad doesn't even exist. Department of Health and Human Services—HHS—regulations call for a permanent ethics advisory board—the EAB—to advise the Secretary of bioethics issues. The EAB has been without members since 1979, supplanted by a series of temporary commissions to study particular bioethics problems. The latest, the National Bioethics Advisory Commission—the NBAC—was directed in 1995 to make their first priority protection of the rights and welfare of human research subjects. Only recently staffed, the commission has now been directed by the President to focus their attention on cloning, and will not review ethical issues arising from specific research projects.

Given these constraints, can the NBAC function in the role envisioned by the permanent Ethics Advisory Board? The weakness of the current system became more apparent recently when the NIH had to convene an ad hoc panel to review serious ethical questions presented by a proposed randomized needle exchange study in Alaska. Intravenous drug users are at high risk of contracting hepatitis and AIDS. For some, participation in the study to increase the avoidable risk of getting hepatitis B, for which there is an effective vaccine. A series of reviews by the local IRB and NIH failed to correct that ethical deficiency or detect flaws in the proposed informed consent materials.

This self-policing, self-validating, and in some ways self-satisfied system of bioethics review and enforcement may be vulnerable to institutional pressures to conform and to cronyism. Missing are the periodic evaluations and external oversight needed to maintain a rigorous bioethical review system. We begin our part of that external oversight today. And we look to our witnesses for suggestions to improve patient protections and informed consent procedures. At this time I would recognize the ranking member and an equal partner in this effort, Mr. Towns.

[The prepared statement of Hon. Christopher Shays follows:]

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Statement of Rep. Christopher Shays
May 8, 1997

Next week the President will formally apologize to the survivors of the 40-year Tuskegee Experiment, a federally funded study in which black men were allowed to suffer and die of a curable disease - syphilis - in the name of scientific research. Last week, this subcommittee heard testimony from Gulf War veterans ordered to take a potentially toxic drug for an experimental use without being informed of any possible side effects. The road from Tuskegee to Baghdad is lined with other landmarks of scientific arrogance and human tragedy -- thalidomide, radiation experiments, the EZ measles vaccine trials.

Those notorious lapses in the protection of human research subjects, and the complex ethical implications of emerging biomedical issues like cloning, gene therapies and AIDS vaccine trials, compel us to ask:

- How effective are current mechanisms to review ethical issues and detect violations of informed consent requirements?
- What needs to be done so patient protections keep pace with scientific advances?
- Do we need a permanent national panel to serve as the arbiter of biomedical ethics issues?

Physicians have a moral duty to inform human research subjects of the foreseeable risks of participation, and a duty to minimize those risks. The discipline of bioethics has evolved from the Hippocratic Oath, to the Nuremburg Code, to current national and international standards to protect the health and human dignity of all who submit themselves to help advance scientific knowledge.

But the current system of bioethical review appears to be showing signs of age and disrepair. Multiple layers of review and enforcement provide a false sense of security that difficult issues are being confronted. The regulatory scheme lacks specific provisions to protect mentally ill, drug addicted and cognitively impaired persons involved in biomedical research.

Local Institutional Review Boards (IRBs), considered the cornerstone of the entire bioethics review structure, are often hard-pressed to monitor research protocols and informed consent procedures on an ongoing basis. By one recent estimate, more than half the federally funded research projects inspected by the FDA between 1977 and 1995 failed in some way to inform research subjects fully of the experimental nature of the medical procedure. Multi-site research studies further challenge the capacity of local IRBs to control the research nominally under their purview.

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This self-policing, self-validating and in some ways self-satisfied system of bioethical review and enforcement may be vulnerable to institutional pressures to conform and to cronyism. Missing are the periodic evaluations and external oversight needed to maintain a rigorous bioethical review system.

We begin our part of that external oversight today, and we look to our witnesses for suggestions to improve patient protections and informed consent procedures.

Welcome.

Mr. TOWNS. Thank you very much, Mr. Chairman. African-Americans have had a long and unhappy history of involuntary participation in medical studies. From 1932 to 1972, U.S. Public Health Service embarked on a 40-year study of African-American men who had contracted syphilis. Known as the Tuskegee Study, the Government agency withheld treatment and administration of a cure in order to study the effects of the disease on the black male. In the 1950's, a University of Cincinnati Medical Center exposed 82 charity ward patients to 10 times the amount of radiation that was known to be safe at the time.

In this study on the effects of full body radiation, three-quarters of the patients in the study were low income black men and women. Their consent signatures had been forged. During the 1970's, one group of parents in Baltimore thought they were enrolling their boys in a free child program at John Hopkins University. During the course of these 3 years, NIH-funded study of 7,000 boys, over 90 percent African-American, had their blood drawn. This blood was subjected to genetic testing without the knowledge or consent of any of the parents.

This long and troubling history has made the African-American community extremely leery of medical research, and let me also add, the medical community. Although representing about 15 percent of the general population, they account for only about 2 to 4 percent of volunteers in cancer prevention trials. For instance, overall, African-Americans have lower cancer survival rates than whites. However, blacks who participate in clinical trials have survival rates equal to those of whites.

In some instances, this unwillingness to participate in trials may hamper later treatment. There is a lot of evidence that racial minorities and other vulnerable groups have been exploited doing medical research. I believe it is the powerlessness of these groups which make them targets for medical exploitation. Surely we cannot allow some members of this society to be sacrificed for the health and well-being of others.

On the other hand, there's evidence that research improves the overall health of the population. We must strike the right balance and ensure that any opportunity for exploitation is eliminated. Current Federal guidelines require the inclusion of women and minorities in clinical research to ensure that biomedical and behavior research findings are applicable to all populations. Therefore, the HHS, CDC, NIH, and FDA must ensure active recruitment of volunteers in minority communities.

However, the Federal Government must also ensure that researchers and research facilities fairly represent the American people. Federal reviewers and local review boards should become suspicious when minorities seem to be purposely excluded or seem to be the exclusive subjects. We may be able to accomplish these modest goals by enacting additional safeguards to protect the rights of the patient. We may need to expand the membership on the institutional review boards, provide additional advocates for patients, include greater participation by those not associated with the research facilities and provide a Federal ombudsman specifically to receive questions or complaints of study participants.

I hope that this hearing does not advocate eliminating Federal research support or placing regulatory restrictions on the receipt of Government funding for research that few institutions are able to meet. I don't want to see that happen. I hope that we can use this opportunity today to build on the existing framework of the Federal regulations to improve our system for the benefit of all future patients and study participants. That's what I hope to accomplish. Mr. Chairman, thank you for raising this important issue—and it is important. I look forward to working with you on this issue and hearing the testimony of today's witnesses, to determine in terms of what we can do to correct the wrongs and to try to move forward by making them right. Thank you so much.

Mr. SHAYS. I thank the gentleman. At this time the Chair recognizes Mr. Pappas, Congressman Pappas from New Jersey.

Mr. PAPPAS. Thank you, Mr. Chairman. I want to thank you for calling this hearing and focusing on an issue that I think more and more Americans are becoming concerned about. The examples that both you and the ranking member, Mr. Towns, mentioned both about the Tuskegee experiment as well as that which some of our Persian Gulf war veterans may have experienced. I'll just point out that the ends do not always justify the means. And there are many people in our country that have a great deal of concern that in folks' overzealousness and excitement with regard to the advances that are being made in research that people could not necessarily just be helped by some of the research and advances that are taking place. So I welcome the opportunity to hear from the panelists here today. Thank you.

Mr. SHAYS. I thank the gentleman. Congressman Kucinich of Ohio.

Mr. KUCINICH. Thank you very much, Mr. Chairman and members of the committee. I want to thank the Chair for holding a hearing on this subject, join with Mr. Pappas' comments, and also express my concern with my good friend Congressman Towns about the way in which minorities are treated on issues like this. The central concern of my constituents is, can public trust and confidence be maintained in such programs? We're concerned about how risks are identified and how they're communicated to human subjects. All of us clearly understand that medical technology and research is part of the unfolding of the possibilities for improved public health.

But we also know that we have a moral and ethical responsibility to see to it that anyone participating in any type of experiment receives the information that they need so that they know what the risks are and that they know what their rights are. There are ethical issues that we'll be reviewing today. And we want to see the extent to which violations of informed consent requirements, whether those requirements were ethical, or in fact rules and regulations may have been violated. It's very clear this is an area of public policy that the Federal Government needs to step up to.

A few years ago we had a couple of laws which regulated bioethics. The National Commission for the Protection of Human Subjects of Biomedical Research and also the President's Commission for the Study of Ethical Providence in Medicine and Biomedical and Behavioral Research were established. Neither are in existence

today. And with the exception of the common rule, which only applies to Federal agency, there's no provision of U.S. law explicitly requiring informed consent and independent review of research involving human subjects.

As we review the biomedical ethics questions here today I am confident that this committee with the cooperation of those who will be testifying will be able to lead the way to establishing some new standards which will derive from ethical considerations. And I'm very grateful, Mr. Chairman, that you have chosen this moment to bring this issue to the forefront.

Mr. SHAYS. I thank the gentleman. And we are joined by the vice-chairman of the subcommittee, Mr. Snowbarger, who is from Kansas and would just as soon we get on with the hearing. So we're going to do what we do at all our hearings. We swear in our witnesses, including any Member of Congress, who come and testify. So if you would stand and raise your right hands, we'll swear you in.

[Witnesses sworn.]

Mr. SHAYS. Thank you. Note for the record that our witnesses have responded in the affirmative. And I will tell you who our witnesses are for the record. We have Dr. William Raub, acting executive director, National Bioethics Advisory Committee and Deputy Assistant Secretary, Department of Health and Human Services. We have Dr. David Satcher, Director, Center for Disease Control and Prevention. We have Dr. Harold Varmus, who is Director, National Institutes of Health. And we have Mary Pendergast, who is Deputy Commissioner, Food and Drug Administration.

I would prefer that we go in the order that I mentioned our witnesses: Dr. Raub, Dr. Satcher, then Dr. Varmus, and then Ms. Pendergast. We'll go in that order. And we don't have our traditional clock. We have asked that you speak for about 5 minutes. But we do recognize that this is a very important subject. And we do want your testimony on the record.

We will just deal with two housekeeping issues and ask unanimous consent that the members of the subcommittee be permitted to place any opening statement in the record and that the record remain open for 3 days for that purpose. And without objection, so ordered. I also ask unanimous consent that all witnesses be permitted to include their written statements in the record. And without objection, so ordered.

Your testimony is important. And we want to make sure that we cover it. So if you go over, a little over the 5 minutes, we recognize, because this is a very important subject. I just say for the four witnesses that will be following, we're happy to have you listen to some of the questions that are asked of the first panel and include them in your opening statements as well. So if you want to just make some notes and so on, that's fine as well. So we'll start with you, Dr. Raub, and welcome.

Mr. RAUB. Thank you, Mr. Chairman.

Mr. SHAYS. Maybe since you haven't started it would make sense for us to vote and then come back. And then we won't have the interruption. And I might say if we have any students here, we will allow students to sit in those first three seats there to give a little

more room. So we'll be back. We stand at recess. And we will hustle.

[Recess.]

Mr. SHAYS. I feel I have tremendous power with this. What I'd like to do, I understand that some of our witnesses have others who have accompanied them who might assist them in responding to questioning, which we actually would want to encourage. But we do need to swear them in. So if any of you have someone you would like to respond to a question, I think it would be good to take care of that now. So do any of you have a witness that might——

Mr. RAUB. Yes, we do.

Mr. SHAYS. Would you identify who they might be? They can just stand where they are for now. Here's what we're going to have to do. We will swear all of you in. And then if you do testify for the recorder, we'll then ask you to give your name then. Let's do it that way. And I'll try to remember faces.

[Witnesses sworn.]

Mr. SHAYS. Thank you very much. I really appreciate your cooperation in this regard. And then if you testify, if you would be prepared just to leave your full name and title for our recorder so he makes sure that he has it. Dr. Raub, we welcome your testimony and you're on.

STATEMENTS OF WILLIAM RAUB, DEPUTY ASSISTANT SECRETARY FOR SCIENCE POLICY, DEPARTMENT OF HEALTH AND HUMAN SERVICES; DAVID SATCHER, CENTERS FOR DISEASE CONTROL AND PREVENTION; HAROLD VARMUS, DIRECTOR, NATIONAL INSTITUTES OF HEALTH; AND MARY PENDERGAST, DEPUTY COMMISSIONER, FOOD AND DRUG ADMINISTRATION

Mr. RAUB. Thank you, Mr. Chairman, and good morning.

Mr. SHAYS. Good morning.

Mr. RAUB. I'm the Deputy Assistant Secretary for Science Policy within the Office of the Assistant Secretary for Planning and Evaluation in the Department of Health and Human Services. I also serve as the acting executive director of the National Bioethics Advisory Commission, heretofore labeled as NBAC, pending completion of recruitment for that position. I appreciate this opportunity to present background information on NBAC and to describe its current activities.

President Clinton established NBAC by Executive order dated October 3, 1995. The order describes that function as follows:

(a) NBAC shall provide advice and make recommendations to the National Science and Technology Council and to other appropriate government entities regarding the following matters:

(1) the appropriateness of departmental, agency or other governmental programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior; and

(2) applications, including the clinical applications of that research.

(b) NBAC shall identify broad principles to govern the ethical conduct of research, citing specific projects only as illustrations for such principles.

(c) NBAC shall not be responsible for the review and approval of specific projects.

(d) In addition to responding to requests for advice and recommendations from the National Science and Technology Council, NBAC also may accept suggestions of issues for consideration from both the Congress and the public. NBAC also may identify other bioethical issues for the purpose of providing advice and recommendations, subject to the approval of the National Science and Technology Council.

The order also indicates that NBAC will terminate on October 3, 1997 unless extended prior to that date.

The Assistant to the President for Science and Technology issued the charter for NBAC in July 1996. In describing the functions of NBAC the charter indicates the following:

> As a first priority, the Commission will direct its attention to consideration of:
> A. Protection of the rights and welfare of human research subjects; and
> B. Issues in the management and use of genetic information including but not limited to human gene patenting.

Also in July 1996, the President appointed the members of NBAC. The chairman is Harold T. Shapiro, Ph.D., president of Princeton University.

NBAC held its first meeting on October 4, 1996. Following a series of background presentations and a general discussion of the President's charge to NBAC, Chairman Shapiro elected to create two subcommittees. The human subjects subcommittee, chaired by James Childress, Ph.D., of the University of Virginia, has the responsibility for examining the current system of protections for human research subjects with emphasis on determining whether research sponsors and performers are adhering to the so-called "common rule"—that is, a set of essentially identical regulations issued simultaneously by 16 agencies of the Federal Government on July 18, 1991—and whether the rule itself is adequate to assess the ethical issues associated with current and future research endeavors. The genetics subcommittee chaired by Thomas H. Murray, Ph.D., of Case Western Reserve University has responsibility for examining the management and use of genetic information with emphasis on the bioethical issues associated with the use of human tissue samples in genetics research.

Each of the two subcommittees has held a series of meetings toward fulfillment of their respective tasks. They have identified information needs, discussed alternative strategies for meeting them, and set priorities for followup efforts by individual commissioners and/or NBAC staff. For example, as both subcommittees identify leading experts from relevant disciplines from whom they wish to receive oral and/or written testimony, NBAC staff make the requisite contractual and logistical arrangements.

In addition, with respect to the assessment of the common rule, a DHHS staff group, with guidance from the human subjects subcommittee, is gathering pertinent information from the participating agencies so that the subcommittee and ultimately the full NBAC will have a strong data base and set of analyses to facilitate its assessment as to how well the system of protection for human research subjects is working. As I will describe in more detail in a few minutes, President Clinton's request for a study of the legal and ethical issues associated with cloning technology added a substantial task to NBAC's agenda, one that demands and is receiving intensive effort from all the commissioners.

This unforeseen development cause both subcommittees to reformulate their work plans for this year with the view to making them less labor- and time-intensive than they otherwise would have been. Nevertheless, both subcommittees are intent upon important substantive contributions in their respective areas in a sufficiently timely manner so that by October 1997, the full NBAC can

report findings and recommendations regarding human subjects protection and genetic testing over and beyond whatever findings and recommendations it provides within the next few weeks with respect to cloning.

NBAC's operating priorities for this year changed abruptly in the wake of the press announcements on February 23, 1997, that scientists in Scotland had cloned a lamb from a single cell from the mammary tissue of a 6-year-old ewe. The scientists' research report appeared in that week's edition of the scientific journal *Nature.* On February 24, President Clinton sent a letter to NBAC Chairman Shapiro, requesting that the National Bioethics Advisory Commission undertake a thorough review of the legal and ethical issues associated with the use of this technology—namely, cloning—and report back to him within 90 days with recommendations on possible Federal actions to prevent its abuse.

Further, on March 4, President Clinton issued to the heads of executive departments and agencies a memorandum entitled, "Prohibition on Federal Funding for Cloning of Human Beings." In that memorandum he mentioned his assignment to NBAC, noting that cloning technology offers the potential for enormous scientific breakthroughs that could offer benefits in such areas as medicine and agricultural while raising profound ethical issues, particularly with respect to its possible use to clone humans.

Since February 25, NBAC has devoted an extraordinary effort toward fulfilling President Clinton's request. The commissioners quickly developed a preliminary framework for the issues they wished to address and organized themselves into several informal working groups so that they initially could pursue various subsets of these issues in parallel. Then they identified within each issue area the specific topics for which they desired additional information, and they provided guidance to NBAC staff regarding leading experts in relevant scientific or professional disciplines who might be sources of or at least links to sources of such information.

Using this guidance, NBAC staff contracted for a series of special analyses on a variety of topics including the state of the science related to cloning, the current array of State and local level statutes that might affect cloning and/or cloning related research, and the historical experience with moratoria associated with other areas where rapid scientific advances raised major ethical issues—that is, fetal research, gene therapy, and recombinant DNA research.

Further, NBAC staff invited experts in science, religion, ethics and other relevant subject matter areas to address the commission directly and participate in indepth discussions of critical issues. Moreover, NBAC staff made special efforts to accommodate within each meeting agenda those members of the public who requested an opportunity to address the commission. To date the full NBAC has held three meetings largely or wholly devoted to the cloning assignment.

Between meetings, the informal subgroups have pursued their respective assignments through special meetings, conference calls or e-mail exchanges, and the NBAC staff has maintained regular, often daily contact with Chairman Shapiro and the other commissioners in anticipation of their needs for assistance or in response to specific requests. The commissioners are optimistic that they can

produce a thorough, well reasoned report to President Clinton on or about the end of this month.

The NBAC charter assigns to the Department of Health and Human Services the responsibility for providing management and administrative support services for NBAC. Secretary Shalala initially delegated this responsibility to the Director, National Institutes of Health, who redelegated it to the Director, Office for the Protection from Research Risks. The Director, OPRR established the NBAC office, recruited the initial complement of staff, and participated with them and Chairman Shapiro in planning and implementation of the initial NBAC activities.

During the fall 1996, the Director, NIH expressed concern that the organizational placement of the NBAC office could create the appearance of conflict of interest. That is, because NBAC inevitably will focus on many issues that fall within the purview of the OPRR, any NBAC assessments that relate to OPRR's activities, whether favorable or otherwise, might lack credibility in the eyes of some observers. After weighing these concerns, Secretary Shalala, on November 1, 1996, reassigned responsibility for NBAC management and administrative support to the Assistant Secretary for Health, who in turn requested that I provide day to day oversight of the NBAC staff in my capacity as his science advisor.

Subsequently, I also assumed the role of acting executive director, pending the recruitment of an appropriately qualified individual to fill this position on a regular basis. And I arranged for a DHHS staff member thoroughly experienced in working with advisory commissions to serve as Acting Deputy Director. The Department recently published the vacancy announcement for the position of NBAC executive director. The position is classified within the senior executive service, and, depending upon the qualifications of the individual selected, offers an annual salary in the range of $104,000 to $120,000 and possibility higher if the individual selected is a physician.

We expect significant competition for this vacancy and look forward to receipt of applications by the deadline, June 4, 1997. The NBAC staff currently consists of eight full-time and four part-time individuals. As NBAC activities continue to evolve, future staffing needs will be assessed by the executive director in consultation with Chairman Shapiro and in context of available resources.

The budget for NBAC this year is approximately $1.6 million. Almost half of those funds—$760,000—are being provided by agencies of the U.S. public health service, namely the NIH, the CDC, the FDA and the Agency for Health Care Policy and Research. The remainder of the funds—$850,000—are being provided by six other departments or agencies, namely the Department of Defense, the Department of Veterans Affairs, the Department of Energy, the Department of Agriculture, the National Aeronautics and Space Administration, and the National Science Foundation. The Office of Science and Technology Policy within the executive office of the President was instrumental in facilitating the arrangements for joint funding of NBAC.

Mr. Chairman, I know that I speak for my colleagues as well as

myself in saying that we are eager to facilitate the work of NBAC as best we can, and that we feel privileged to work with this capable and dedicated group of commissioners. If you have questions I will be pleased to respond either now or for the record.

[The prepared statement of Mr. Raub follows:]

1

Good morning, Mr. Chairman. My name is William F. Raub. I am the Deputy Assistant Secretary for Science Policy within the Office of the Assistant Secretary for Planning and Evaluation, Department of Health and Human Services. I also am serving as the Acting Executive Director of the National Bioethics Advisory Commission (NBAC), pending completion of recruitment for that position. I appreciate this opportunity to present background information on NBAC and to describe its current activities.

Establishment of NBAC

President Clinton established NBAC by Executive Order dated October 3, 1995. The Order describes the functions as follows:

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c) NBAC shall not be responsible for the review and approval of specific projects.

(d) In addition to responding to requests for advice and recommendations from the National Science and Technology Council, NBAC also may accept suggestions of issues for consideration from both the Congress and the public. NBAC also may identify other bioethical issues for the

purpose of providing advice and recommendations, subject to the approval of the National Science and Technology Council."

The Order also indicates that NBAC will terminate on October 3, 1997 unless extended prior to that date.

The Assistant to the President for Science and Technology issued the Charter for NBAC in July, 1996. In describing the functions of s the following:

"As a first priority, the Commission will direct its attention to consideration of:

A. Protection of the rights and welfare of human research subjects; and

B. Issues in the management and use of genetic information including but not limited to human gene patenting."

Also in July, 1996, the President appointed the members of NBAC. The Chairman is Harold T. Shapiro, Ph.D., President of Princeton University.

Initial Activities of NBAC

NBAC held its first meeting on October 4, 1996. Following a series of background presentations -- including remarks by the Assistant to the President for Science and Technology, other Executive Branch staff, a legislative assistant to former Senator Hatfield and the minority staff director of the Senate Committee on Governmental Affairs -- and a general discussion of the President's charge to NBAC, Chairman Shapiro elected to create two subcommittees. The Human Subjects Subcommittee, chaired by James Childress, Ph.D. of the University of Virginia, has responsibility for examining the current system of protections for human research subjects -- with emphasis on determining whether research sponsors and performers are adhering to the so-called "Common Rule" (i.e., a set of essentially identical regulations issued simultaneously by 16

agencies of the Federal Government on July 18, 1991) and whether the rule itself is adequate to assess the ethical issues associated with current and future research endeavors. The Genetics Subcommittee, chaired by Thomas H. Murray, Ph.D., of Case Western Reserve University, has responsibility for examining the management and use of genetic information -- with emphasis on the bioethical issues associated with the use of human tissue samples in genetics research.

Each of the two subcommittees has held a series of meetings toward fulfillment of their respective tasks. They have identified information needs, discussed alternative strategies for meeting them, and set priorities for follow-up efforts by individual commissioners and/or NBAC staff. For example, as both subcommittees identify leading experts from relevant disciplines from whom they wish to receive oral and/or written testimony, NBAC staff make the requisite contractual and logistic arrangements. In addition, with respect to assessment of the Common Rule, a DHHS staff group -- with guidance from the Human Subjects Subcommittee -- is gathering pertinent information from the participating agencies so that the subcommittee and, ultimately the full NBAC, will have a strong data base and set of analyses to facilitate its assessment as to how well the system for protection of human research subjects is working.

As I will describe in more detail in a few minutes, President Clinton's request for a study of the legal and ethical issues associated with cloning technology added a substantial task to NBAC's agenda -- one that demands and is receiving intensive effort from all the Commissioners. This unforeseen development caused both subcommittees to reformulate their work plans for this year with a view to making them less labor- and time-intensive than they otherwise would have been. Nevertheless, both subcommittees are intent upon providing important substantive contributions in their respective areas in a sufficiently timely manner so

that, by October, 1997, the full NBAC can report findings and recommendations regarding human-subjects protection and genetic testing over and beyond whatever findings and recommendations it provides within the next few weeks with respect to cloning.

NBAC Study of Issues associated with Cloning Technology

NBAC's operating priorities for this year changed abruptly in the wake of press announcements on February 23, 1997 that scientists in Scotland had cloned a lamb from a single cell from the mammary tissue of a six-year-old ewe. The scientists' research report appeared in that week's edition of the scientific journal Nature. On February 24, President Clinton sent a letter to NBAC Chairman Shapiro requesting that "the National Bioethics Advisory Commission undertake a thorough review of the legal and ethical issues associated with the use of this (cloning) technology and report back to me within ninety days with recommendations on possible federal actions to prevent its abuse". Further, on March 4, President Clinton issued to the Heads of Executive Departments and Agencies a memorandum entitled "Prohibition on Federal Funding for Cloning of Human Beings". In that memorandum, he mentioned his assignment to NBAC -- noting that cloning technology offers the potential for "enormous scientific breakthroughs that could offer benefits in such areas as medicine and agriculture" while raising "profound ethical issues, particularly with respect to its possible use to clone humans".

Since February 25, NBAC has devoted an extraordinary effort toward fulfilling President Clinton's request. The Commissioners quickly developed a preliminary framework for the issues they wished to address and organized themselves into several informal working groups so that they initially could pursue various subsets of these issues in parallel. They then identified within each issue area the specific topics for which they desired additional information; and they

provided guidance to NBAC staff regarding leading experts in relevant scientific or professional disciplines who might be sources of -- or at least links to sources of -- such information.

Using this guidance, NBAC staff contracted for a series of special analyses on a variety of topics including the state of the science related to cloning, the current array of state- and local-level statutes that might affect cloning and/or cloning-related research, and the historical experience with moratoria associated with other areas where rapid scientific advances raised major ethical issues -- i.e, fetal research, gene therapy, and recombinant DNA research. Further, NBAC staff invited experts in science, religion, ethics, and other relevant subject-matter areas to address the Commission directly and participate in in-depth discussion of critical issues. Moreover, NBAC staff made special efforts to accommodate within each meeting agenda those members of the public who requested an opportunity to address the Commission.

To date, the full NBAC has held three meetings largely or wholly devoted to the cloning assignment: March 13-14, April 13, and May 2. Between meetings, the informal subgroups have pursued their respective assignments through special meetings, conference calls, or EMAIL exchanges; and the NBAC staff has maintained regular, often daily, contact with Chairman Shapiro and the other Commissioners in anticipation of their needs for assistance or in response to specific requests. The Commissioners are optimistic that they can produce a thorough, well-reasoned report to President Clinton on or about the end of this month.

Management and Administrative Support for NBAC

The NBAC charter assigns to the Department of Health and Human Services the responsibility for providing management and administrative support services for NBAC. Secretary Shalala initially delegated this responsibility to the Director, National Institutes of

Health, who redelegated it to the Director, Office for Protection from Research Risks (OPRR). The Director, OPRR, established the NBAC office, recruited the initial complement of staff, and participated with them and Chairman Shapiro in planning and implementation of the initial NBAC activities.

During the fall of 1996, the Director, NIH expressed concern that the organizational placement of the NBAC office could create the appearance of conflict of interest. That is, because NBAC inevitably will focus on many issues that fall within the purview of the OPRR, any NBAC assessments that relate to OPRR's activities -- whether favorable or otherwise -- might lack credibility in the eyes of some observers. After weighing these concerns, Secretary Shalala, on November 1, 1996, reassigned responsibility for NBAC management and administrative support to the Assistant Secretary for Health (ASH) -- who, in turn, requested that I provide day-to-day oversight of the NBAC staff in my capacity as his Science Advisor. Subsequently, I also assumed the role of Acting Executive Director, pending recruitment of an appropriately qualified individual to fill this position on a regular basis; and I arranged for a DHHS staff member thoroughly experienced in working with advisory commissions to serve as Acting Deputy Executive Director.

The Department recently published the vacancy announcement for the position of NBAC Executive Director. The position is classified within the Senior Executive Service and, depending upon the qualifications of the individual selected, offers an annual salary in the range of $104,000 to $120,000 and possibly higher if the individual selected is a physician. We expect significant competition for this vacancy and look forward to receipt of applications by the deadline -- June 4, 1997.

The NBAC staff currently consists of 8 full-time and 4 part-time individuals. As NBAC activities continue to evolve, future staffing needs will be assessed by the Executive Director in consultation with Chairman Shapiro and in the context of available resources.

The budget for NBAC this year is approximately $1.6 million. Almost half of those funds ($760,000) are being provided by agencies of the U.S. Public Health Service -- namely, the National Institutes of Health, the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Agency for Health Care Policy and Research. The remainder of the funds ($850,000) are being provided by six other Departments or Agencies -- namely, the Department of Defense, the Department of Veterans Affairs, the Department of Energy, the Department of Agriculture, the National Aeronautics and Space Administration, and the National Science Foundation. The Office of Science and Technology Policy within the Executive Office of the President was instrumental in facilitating the arrangements for joint funding of NBAC.

Mr. Chairman, I know that I speak for my colleagues as well as myself in saying that we are eager to facilitate the work of NBAC as best we can and that we feel privileged to work with this capable and dedicated group of Commissioners. If you have questions, I will be pleased to respond either now or for the record.

Mr. SHAYS. Thank you, Doctor. We'll have questions when we've heard from everyone. But you'll be asked questions about why the EAB couldn't be doing this why would you be hiring someone in June when it's going to come to a conclusion in October. To help sort that out for us. Dr. Satcher.

Dr. SATCHER. Thank you, Mr. Chairman and members of the subcommittee. Let me say that I'm pleased to be able to join you for this very important discussion. I think recently I've had opportunities to testify before this subcommittee, dealing with issues such as the safety of the blood supply and the safety of the food supply in this country. I think those are very critical issues for us and I think today's discussion of informed consent is equally critical.

CDC is committed to protecting all persons who agree to participate in research studies. We make every effort to comply fully with the Title 45 Code of Federal Regulations, Part 46 for the protection of human subjects.

Mr. SHAYS. Doctor, I'm going to just ask you to pause a second.

Dr. SATCHER. Sure.

Mr. SHAYS. But we're kind of getting a ring. And I don't know why. It's not your fault. But I'm just wondering in the case of that mic, we'll just pull it away and see if it's——

Dr. SATCHER. OK.

Mr. SHAYS. No. The mic will work—no pull away—just a little further. Yes. Maybe that will help. Let's try it here.

Dr. SATCHER. OK.

Mr. SHAYS. You have such a nice-sounding voice, but we're getting this little echo.

Dr. SATCHER. Well, despite the commitment which we——

Mr. SHAYS. No. I think if you turn that mic away. Let's turn it away. Let's try that. Sorry.

Dr. SATCHER. Despite our commitment and the fact that we make every effort to comply with Title 45 CFR, Part 46 for the protection of human subjects, we are, however, aware of incidents that indicate lapses in our efforts to protect individuals who have participated in research that we have conducted. I'm confident that the corrective actions that we have taken and that we continue to work on will continue to improve our protection of research subjects. I would like to address specifically two examples of these lapses.

First, the EZ measles vaccine study. From 1989 to 1991, the United States experienced a measles epidemic with more than 55,000 cases and more than 120 deaths, mostly in young children, many of them under 1 year of age. Many cases occurred in this age group that was considered too young to be vaccinated with the standard measles vaccine—Moraten. During the 1980's, multiple studies conducted around the world indicated that another vaccine, the Edmonston-Zagreb [EZ] measles vaccine administered at 10- to 100-fold greater potency than the standard dose for measles vaccine, was showing promising results in children under 12 months of age. Because of measles cases and deaths in children less than 12 months of age in this country, CDC undertook a study, in May 1990, of U.S. infants to determine whether results found in other countries could be duplicated in this country. And there were sev-

eral studies in other countries carried out by the World Health Organization. In fact, over 200 million doses of this [EZ] vaccine had been administered. And who had recommended it in cases like this.

Beginning in June 1990, under the auspices of the Kaiser Foundation Research Institute and the Los Angeles County Health Department, approximately 1,500 children were enrolled and randomly allocated into five different study groups and received either higher or standard dosages of EZ vaccine and standard doses of the Moraten vaccine. The protocol for the study was reviewed and approved by the IRB at CDC prior to awarding a contract to Kaiser, and was later approved by the IRB at Kaiser.

The parents or parent's representatives for each child enrolled in the measles study signed the consent form which described the purpose of the study, the procedures to be followed, and the benefits and risks of participation. Thus, the parents of the children who participated in the study were aware that they were participating in a vaccine study. However, we later acknowledged that the consent form was deficient because the EZ measles vaccine was not identified clearly as experimental and parents were not given adequate description of the foreseeable risks of vaccination and alternative treatments.

During the time the EZ measles study was being conducted data became available from a study in Senegal, West Africa suggesting lower survival in girls who received high potency measles vaccine compared to girls who received the standard potency vaccine. So October 1991, as additional information became available from a study of this same high potency measles vaccine in Haiti, suggesting that girls vaccinated with this level of potency were at increased risk of dying in the 2 or 3 years following the vaccination, CDC stopped all use of EZ vaccines in Los Angeles County in October 1991.

Following the termination of the EZ measles vaccine study, all children who participated in the study were asked to enter a followup study to determine whether the vaccine had any adverse health effects. Parents were informed of the reason for the followup study, including the fact that some studies had found lower survival in those children who received high potency vaccine. To date, of all the children who have been evaluated, no child who took part in this study and received the high potency EZ vaccine has suffered a significant health problem that can be associated with the vaccine.

And in fact, the death rate in the group of participants is no different from the rest of the population of children. In a thorough review of this study, the Office of Protection from Research Risks [OPRR] concluded in 1995 that the EZ measles vaccine study was scientifically and ethically justified, however, the consent form was deficient. In response to the recommendations from OPRR, a letter signed by Kaiser Permanente was sent in June 1996 covering the topics required by OPRR and approved by the IRB at both institutions.

In addition, CDC and Kaiser sent a jointly signed letter of apology in September 1996, to the parents of the children enrolled in the trials. In this letter, an apology was made for the mistake on the consent form of the study, acknowledging that the parents who

enrolled their children in the study were not adequately informed. The issue was informed consent.

Now there is another example which I will discuss only briefly. And that has to do with the hepatitis A vaccine prior to its licensure. While the incidence of hepatitis A has declined substantially since 1950, more than 28,000 cases were reported to CDC in 1996. And we estimate that there are about 150,000 cases of hepatitis A in this country each year. American Indians have a rate of hepatitis A infection that is 20 times higher than for whites and African-Americans.

It was anticipated that several American Indian communities in North and South Dakota would have hepatitis A epidemics during the early 1990's. The prevention of hepatitis A has been somewhat problematic and has primarily relied on improvement in hygienic conditions. In the 1980's a number of prototype hepatitis A vaccines were developed and offered the potential to control and prevent the disease. And let me say briefly, in South Dakota, before the hepatitis A trials were launched, there was informed consent on the part of the parents and assent on the part of children over the age of 7.

In addition to the CDC Institutional Review Board, there was also a review by the Indian Health Service Institutional Review Boards. And the tribal councils in South Dakota also had to approve the study as this was the Pine Ridge Reservation in South Dakota. The study was approved in 1990 and over 500 children were enrolled in the study. But in this particular case there was concern expressed by many people early, so only one child was ever vaccinated in South Dakota.

Later, however, in North Dakota on the Standing Rock Reservation—we also implemented a study with the consent of our IRB, the Indian Health Service Institutional Review Board, the tribal councils on the reservations, and, again, the parents and the children. The study began by enrolling 245 children and about 245 children were vaccinated before the study was stopped. The study was stopped, again, because of concern expressed by people on the reservation that this was a study where about 60 percent of the participants were American Indians. And the concern was, why was the study being done on American Indians primarily. So the study was stopped after vaccinating 245 children.

Later, in Thailand, based on some work done by others, it was demonstrated that the hepatitis A vaccine was in fact effective at preventing hepatitis A. Since that time, American Indians have been vaccinated against hepatitis A. And the epidemics that occurred every 5 to 7 years in the past seem to be under control.

Our position is, and I think most who have reviewed these studies agree, that in the case of the hepatitis A—unlike the EZ vaccine—in the case of the hepatitis A there was full informed consent. Not only was it reviewed by the IRBs at CDC and the Indian Health Service, but also the tribal councils approved. However, I think what this points out—and I think it's a very important point that some of you have made—is that because we were dealing with a minority population that often feels that it does not have access to the full value of medical therapy in this country, when a study

disproportionately involves those populations, they often are suspicious. And I think most of us can understand why.

So this study was stopped because of the suspicion of the members of the reservation that they were being selected out for a study. Today, everyone agrees that the hepatitis A vaccine is effective in preventing hepatitis A in a very high percentage of the cases.

Mr. Chairman, I would like to say that there are two things that we would like to leave with you. No. 1, we believe that the systems that we have in place to protect the human subjects are better than they've ever been, but we don't believe that they are good enough. We have invested significantly in upgrading our office of human subject protection. We review the consent forms, and we made sure that there is certain information in every consent form. We require that any researcher at CDC is trained in bioethics and the implications of serving on the institutional review board. And we've had several leadership director's forums to discuss these issues. However, despite all these efforts, much remains to be done and we will continue to work to improve these systems.

However, I think this will be relevant later this morning. There are certain ethical principles about which there will continue to be debate, especially when one ethical principle seems to compete with another. And hopefully we will have an opportunity to discuss that later. Thank you.

[The prepared statement of Dr. Satcher follows:]

INTRODUCTION

Good morning, I am Dr. David Satcher, Director of the Centers for Disease Control and Prevention (CDC).

I am pleased to have the opportunity to testify before the Subcommittee on Human Resources on the very important topic of informed consent in government-sponsored research.

CDC is one of the Federal agencies in the Department of Health and Human Services that is actively engaged in conducting research involving human subjects. CDC conducts public health research which includes, but is not limited to, clinical trials, epidemiologic studies, health status surveys, laboratory studies, and intervention studies. We, therefore, are particularly concerned with protecting human research subjects and in assuring that an informed consent process is used that allows individuals to decide freely whether to participate in a research study.

In thinking about the mission of CDC and the role that research plays in achieving that mission, two points need to be made that relate to this hearing. The first is that we must maintain clear and unwavering respect for the dignity and worth of all individuals. The second is that there is no substitute for good, rigorous science. Our ethics that ensure the rights and welfare of study participants must be as sound as our science.

CDC is committed to protecting all persons who agree to participate in research studies. We believe strongly in the ethical principles that underlie the conduct of research delineated by The

National Commission for the Protection of Human Subjects of Medical and Behavioral Research in The Belmont Report - that individuals are autonomous and are capable of making decisions about their lives, that individuals should be protected from harm, that benefits should be maximized to individuals, and that there is fairness among individuals in the distribution of risks and benefits. We also make every effort to comply fully with Title 45, Code of Federal Regulations, Part 46 for Protection of Human Subjects, known as the Common Rule. We are, however, aware of incidents indicative of lapses in our efforts to protect individuals who have participated in research we have conducted. I am confident that the corrective actions we have taken are working to protect research subjects.

PROTECTION OF HUMAN RESEARCH SUBJECTS

Excellence in science requires a mastery of the ethical principles that address the protection of human subjects and a mastery of the scientific method. We strive for excellence although we have sometimes failed to achieve it. For example, the Department of Health and Human Services continues to deal with the aftermath of the Tuskegee Syphilis Study. This study was conducted by the U.S. Public Health Service in 1932 to 1972 to learn more about untreated syphilis. In so doing, treatment was withheld from a group of poor black men infected with the disease. In addition, the participants were not informed about the study and their voluntary consent to participate was not obtained.

Recognition of the ethical violations committed in this study led the Federal government to delineate ethical principles for guiding research and to develop Federal regulations outlining

policies and procedures for protecting human subjects. Although we are now doing a better job of protecting persons who participate in research, the legacy left from the Tuskegee Syphilis Study continues to affect negatively the willingness of minorities to participate in research. We must learn from this study and move beyond it so that we restore trust in the research process.

I would like to describe to the Subcommittee what CDC does to protect human research subjects. In addition, I will discuss human subject protection issues related to a measles vaccine study we conducted in Los Angeles and two hepatitis A vaccine studies we conducted in North and South Dakota.

There are six institutional review boards (IRBs) that review research protocols that are developed in the various components of CDC and ATSDR. Some of the IRBs are headquartered outside of Atlanta, such as at the National Center for Health Statistics (NCHS) in Hyattsville, Maryland and at the National Institute for Occupational Safety and Health (NIOSH) in Cincinnati, Ohio. The work of the IRBs is coordinated by the Deputy Associate Director for Science to facilitate consistency in protocol review across the IRBs.

When the IRBs review research protocols, they examine the risks associated with the study, the potential benefits, if any, that the study participants may receive, and whether the risks are justified in light of the potential benefits to be gained from the study. They pay careful attention to the selection of subjects, particularly the inclusion of traditionally under-represented

sociodemographic groups, such as women and minorities. How participants are enrolled and how informed consent is obtained are areas of particular concern.

Informed Consent Process

Because informed consent is essential to conducting ethical research, I would like to review the informed consent process and how CDC assures that an effective consent process is used in each research study. Informed consent is a process of interaction between the researcher and the participant that begins when the participant is initially approached to participate in the study. The researcher explains the study and may provide written information about the study. During this phase of the process, the researcher fully discloses information about the study to the potential participant. This is done in a way that the potential participant can understand the information. Often, the potential participant asks questions and seeks out information about the study which may not be included in any written material about the study; research staff then provide that information to the participants. At the point where potential participants believe they understand the study and the researcher believes the potential participants understand the study, the researcher asks the potential participants whether they wish to participate in the study. A written consent form is signed by the participants, unless explicitly waived by the IRB.

The informed consent process does not end at this point, but continues with the researcher providing information to the subject throughout the life of the study. New information is provided as it becomes available and any questions are answered that the subject may have.

Participants may withdraw from the study at any time. In this manner, the consent process is an ongoing exchange of information during the duration of the study.

CDC's IRBs review studies to make certain that an adequate consent process is in place. Although our IRBs focus heavily on the written consent document, they also review all information that accompanies the consent document, including scripts used by researchers to present information verbally about the study. Our IRBs require that certain key elements are included in all consent forms, as specified in the Common Rule. In addition, we require that consent forms be written at a reading level appropriate to the study population, generally at the 8th grade reading level. In studies involving vulnerable populations such as children or incarcerated persons, we take extra precautions such as requiring assent to participate from children 7 years and older as well as parental consent, and we make every effort to ensure that, if incarcerated persons are to be included in a study, they are not coerced to participate.

Improvement in Human Subjects Protection Efforts

In recent years, we have taken several major steps to improve our human subjects protection efforts, some of which pertain directly to obtaining informed consent. Three of the most important steps are as follows. First, we have developed clear and consistent policies and guidelines about protecting human subjects. For example, there is a policy for including women and minorities in research, guidelines for defining research and non-research activities in public health, a policy describing the roles of management for making decisions about human subjects review, and a policy describing what types of research must be reviewed by an IRB. These

policies communicate a clear message about CDC's determination to protect human subjects and the role that investigators, managers and IRB members have in assuring that sound, ethical research is conducted. The policies reinforce the Common Rule and the Belmont Report by stating the rights of individuals to have full disclosure of information related to the study in order to decide whether to participate in the research.

Second, we have increased training on conducting ethical research and protecting human subjects for CDC staff. We have sponsored workshops, and we will be introducing a multimedia, computer-assisted training program. Our training is designed not only to increase knowledge and awareness about the methods to assure the protection of subjects but also to create a workforce that understands, appreciates, and values the rights of human beings who participate in research.

Third, we have changed the composition of our IRBs to assure that members reflect the race, ethnicity, gender, and experiences of the persons who volunteer to be subjects in our studies. By having IRB members who represent the study populations, issues about consent are raised from the study population's perspective and the consent process and consent form can be tailored to meet the needs of the study population.

DISCUSSION OF TWO SPECIFIC CDC RESEARCH STUDIES

Comparative Trial of Different Schedules of Edmonston-Zagreb (EZ) and Moraten Measles Vaccines in the United States (EZ Measles Vaccine Study)

You have asked me to respond to issues of informed consent regarding two specific research

studies conducted by CDC. The first is a measles vaccine study we conducted in Los Angeles between 1990 and 1991, generally known as the EZ measles study. EZ stands for Edmonston-Zagreb, the strain of virus used to make the vaccine. The second are studies of hepatitis A vaccine we conducted in North and South Dakota in 1991 and 1992. I will address the EZ measles vaccine study first.

From 1989-1991, the United States experienced a measles epidemic with more than 55,000 cases and more than 120 deaths, most in young children. Many cases occurred in children too young to be vaccinated with the standard Moraten measles vaccine, which has low efficacy among children younger than 12 months of age, which is the routine age for vaccination in the US.

During the 1980s, multiple studies conducted around the world indicated that EZ measles vaccine administered in a 10- to 100- fold greater potency than the standard dose for measles vaccine, showed promising results in children below 12 months of age. The EZ vaccine was not a new vaccine. It was being produced in several countries, including some European vaccine manufacturers, and approximately 200 million doses of the vaccine had been administered as part of routine immunization programs in many countries. What was new in the United States, however, was its use in children under 12 months of age, as well as its use at a higher potency.

Based on a growing body of evidence, the World Health Organization (WHO) had recommended in 1989 that high potency EZ vaccine be used routinely at 6 months of age in areas where there was a substantial risk of measles mortality among young children. Because of measles cases and

deaths in children less than 12 months old, CDC undertook a study in May 1990 in U.S. infants to determine whether the results found in other countries could be duplicated in this country.

Beginning in June 1990, under the auspices of the Kaiser Foundation Research Institute and the Los Angeles County Health Department, approximately 1500 children were enrolled and randomly allocated into 5 different study groups to receive either high or standard doses of EZ vaccine, or standard doses of the Moraten vaccine. Approximately 1200 children were ultimately vaccinated with one of the study vaccines at either 6, 9, or 12 months of age. The EZ vaccines that were used were approved for investigation by the Food and Drug Administration (FDA) following the procedures that FDA uses to approve any new drug for investigation of safety and efficacy. In addition, the protocol for the study was reviewed and approved by the IRB at CDC prior to awarding a contract to Kaiser Permanente and was later approved by the IRB at Kaiser.

The parent or parent's representative for each child enrolled in the measles study signed the consent form which described the purpose of the study, the procedures to be followed, and the benefits and risks of participation. Thus, the parents of the children who participated in the study were aware they were participating in a vaccine study. However, we later acknowledged that the consent form was deficient because the EZ measles vaccine was not identified as experimental, and parents were not given an adequate description of the foreseeable risks of vaccination and alternative treatments.

During the time the EZ measles study was being conducted, data became available from a study in Senegal, West Africa, suggesting lower survival in girls who received high potency measles vaccines compared with girls who received standard potency vaccines. In November 1990, CDC staff attended a meeting in Senegal to review the status of the Senegal measles vaccine study. It was recommended at that time, that WHO should convene a group of independent consultants to review data from the study and other similar studies.

In February 1991, WHO convened a panel of experts to review data from studies in Senegal and Guinea Bissau which showed lower survival in girls (but not boys) who received high potency measles vaccines; studies in other locations, however, showed no differences in survival. The WHO concluded that the data did not support a change in the recommendation to continue use of high potency measles vaccines. Reasons were that the studies were not designed to assess mortality, the statistical methods limited interpretation, there was no specificity in the causes of deaths, and the disproportionate mortality in girls did not have biological plausibility. In May 1991, CDC consulted with outside experts who reviewed the evidence from the studies showing lower survival in children who received high potency vaccines and the experts recommended that the Los Angeles measles vaccine study should be continued.

In October 1991, additional information became available from a study of high potency measles vaccine in Haiti which suggested that girls vaccinated with the higher potency measles vaccines were at increased risk of dying in the two to three years following vaccination. No serious adverse effects were attributed to standard potency vaccines, including EZ. Because of this

additional information on high potency measles vaccine, CDC stopped all use of EZ vaccine in the Los Angeles study in October 1991. Eight months later, in June 1992, the World Health Organization reached a similar conclusion and recommended that high potency measles vaccines of any strain should not be used to vaccinate children. EZ vaccine in standard doses continues to be used around the world.

Following the termination of the EZ measles vaccine study, all children who participated in the study were asked to enter a follow-up study to determine whether the vaccine had any adverse health effects. Parents were informed of the reason for the follow-up study, including the fact that some studies had found lower survival in those children who received the high potency vaccine. Most have been medically followed and evaluated until reaching fours years of age.

To date, of all the children who have been evaluated, no child who took part in this study and received the high potency EZ vaccine has suffered a significant health problem that can be associated with the vaccine. CDC estimates that 95 percent of the children who were followed up and revaccinated have serologic evidence of protection against measles. One child died approximately 1 year after receiving a dose of standard potency EZ measles vaccine. Experts reviewed the death certificate, the circumstances surrounding the death, and the autopsy report and all agreed with the conclusion that the death was in all likelihood unrelated to the vaccine. Standard potency measles vaccine has never been associated with higher mortality in any of the vaccine studies. Recently, CDC working with Kaiser has conducted a special mortality search to

identify children who were in the study and died. A second death has been identified due to child abuse. The child had received the Moraten vaccine at 12 months of age.

In a thorough review of this study, the Office for Protection from Research Risks (OPRR) concluded in 1995 that the EZ measles vaccine study was "scientifically and ethically justified" however, the consent form was deficient because it failed to include a) an adequate explanation of the purposes of the research and identification of the EZ vaccine as experimental, b) an adequate description of the foreseeable risks of the experimental EZ vaccine and the standard Moraten vaccine, and c) adequate disclosure or description of alternative treatments. Parents were informed that any new vaccine may have side effects and risks which are currently unknown and unforeseeable; however, they were not told specifically about the potential risk of a failure to be protected by the vaccine. Instead, parents were told that if their child was not protected, he/she would receive a dose of the standard Moraten vaccine.

In light of these findings, OPRR required that a letter be sent to the parents describing the current status of the research, plans for completion of the research and notification of subjects about results, and any reasonably foreseeable future risks of participation in the research. In response to the recommendations from the OPRR report, a letter signed by Kaiser Permanente was sent in June 1996 covering the topics required by OPRR and approved by the IRB's at both institutions. In addition, CDC and Kaiser Permanente sent a jointly signed letter of apology in September 1996 to the parents of the children enrolled in the study. In this letter, an apology was made for the

mistake on the consent form of the study, acknowledging that the parents who enrolled their children in the study were not adequately informed.

CDC, in collaboration with Kaiser Permanente, is continuing follow-up of children who participated in the original study and analysis is ongoing. Analyses are expected to be completed by the summer of 1997, at which time CDC will convene a group of experts to review the results. Following the experts' review, CDC will inform parents about the conclusions from the study.

We acknowledge that we were in error by not fully informing parents of children who participated in the EZ measles vaccine study. In addition to the steps taken to inform parents and following the report of OPRR, CDC developed written information for investigators about the IRB review process which included a checklist of elements to be included in consent forms. The number of IRBs was increased, an additional member from the community was added to each board, the number of staff who work with the IRBs was increased, and training on human subject protections was implemented.

Evaluation of the Safety, Immunogenicity and Protective Efficacy of an Inactivated Hepatitis A Vaccine in Healthy Children (North and South Dakota)

Now I would like to discuss the studies CDC and its collaborators conducted to evaluate the performance of inactivated hepatitis A vaccine prior to its licensure. These studies were done primarily among American Indian populations living in North and South Dakota.

Prior to 1970, nationwide epidemics of hepatitis A occurred approximately every 10 years and approximately 50 percent of persons born before 1950 have been infected. While the incidence of hepatitis A has declined substantially since the 1950's, more than 28,000 cases were reported to CDC in 1996. CDC estimates that more than 150,000 Americans are infected with hepatitis A virus each year. Most people become infected because of community-wide epidemics that often go on for several years. In addition, rates of hepatitis A vary among racial and ethnic groups. American Indians and Alaska Natives have a rate of hepatitis A infection that is 20 times higher than for whites and African Americans. Epidemics of hepatitis A occur approximately every 6 to 8 years in American Indian and Alaska Native communities throughout the United States, and more than 80 percent of adults in these populations have been infected with the hepatitis A virus.

Prevention of hepatitis A has been somewhat problematic and has primarily relied on improvements in hygienic conditions, including improved waste disposal, food sanitation, and general living conditions. Until recently, the only immunization against hepatitis A was the use of immune globulin, which only provided short-term protection and was not useful in preventing community-wide epidemics. In the 1980's, a number of prototype hepatitis A vaccines were developed and offered the potential to control and prevent this disease.

The most widely evaluated hepatitis A vaccines have been those produced in the same manner as inactivated polio vaccine -- hepatitis A virus is grown in tissue culture and is then inactivated (killed) and formulated into a vaccine. In the late 1980's, experts in hepatitis questioned whether the immunity produced by inactivated hepatitis A vaccine would protect against hepatitis A in

human populations. This question and the best means to evaluate the protective efficacy of hepatitis A vaccine were discussed at several meetings, including an international meeting of hepatitis, public health, and infectious disease experts which was co-sponsored by NIH and CDC in November 1989. The consensus among the experts was that double-blind, placebo-controlled clinical trials should be conducted to determine the protective efficacy of hepatitis A vaccines. To determine whether these vaccines protected against infection and/or disease, these studies had to be carried out in populations that experienced high rates of hepatitis A virus infection. Since these studies had to be carried out when these infections were occurring and because high rates of hepatitis A do not occur uniformly over time, the best time to perform these studies was during a community-wide epidemic.

As I previously indicated, CDC's national surveillance for viral hepatitis showed that the highest rates of hepatitis A were in American Indian/Alaska Native populations. In addition, CDC and Indian Health Service (IHS) epidemiologists had collaboratively characterized the epidemiology of hepatitis A among various Native American populations. They had identified these high rates of infection and the recurrent nature of community-wide epidemics in these populations, and they had accurately predicted when these epidemics would occur in some of these communities. It was anticipated that several American Indian communities in North and South Dakota would have hepatitis A epidemics during the early 1990's. The evaluation of hepatitis A vaccine in controlled clinical trials during those predicted epidemics could determine the vaccine's efficacy, its potential to provide long-term protection against hepatitis A, and its potential to control these epidemics.

These epidemiologic issues and the logistics of such trials were discussed in a 1989 meeting of CDC epidemiologists and laboratory scientists, IHS clinicians and epidemiologists, and scientists from the vaccine manufacturers. It was the predicted recurrence of epidemic hepatitis A on reservations in the IHS Aberdeen Area in South and North Dakota and the need to determine the efficacy of inactivated hepatitis A vaccine in preventing hepatitis A that led to the collaborative effort between CDC, IHS and SmithKline Beecham (SKB).

The study was designed to determine the efficacy of inactivated hepatitis A vaccine in protecting 3 to 12 year-old children against hepatitis A. Children participating in the study were to receive either the investigational, unlicensed (for commercial use) hepatitis A vaccine or the licensed hepatitis B vaccine produced by SKB. Because hepatitis B vaccine does not provide protection against hepatitis A, it was used as a placebo treatment in the study. The protocol, the consent forms, and the informational materials were reviewed and approved by the CDC and IHS IRBs. The study was also approved by the IHS Aberdeen Area Research Committee.

Participation in the study was voluntary and only occurred after the child's parent provided written informed consent, and children 7 years and older gave assent. In addition to the requirement of individual informed consent for participation, it was also required that all studies conducted among American Indians be approved by the local tribal council or health board. This was also done for these studies. In obtaining consent for participation in the study, every effort was made to ensure that the parents understood the reason for the study, the potential risks and benefits of the study, and what was expected if their child participated. They were told the

number of shots their child would receive, the number of blood specimens that would have to be drawn, and that neither they nor the study nurse would know which vaccine was being given to their child until the study was completed or unless the child experienced an adverse event. While most of the informational material was written in English, some materials were written in the Lakota language. In addition, most of the study nurses were tribal members and Lakota-speaking personnel were available, if needed.

Studies to evaluate the efficacy of inactivated hepatitis A vaccine were initiated on two reservations. The first study was conducted on the Pine Ridge reservation in South Dakota where it was approved by the Pine Ridge Oglala Sioux Tribal Council in June 1990. An estimated 2400 children were needed for the study and recruitment began in April 1991. Written informed consent had been obtained from parents of more than 500 children and assent was also obtained from children 7 years and older when the Pine Ridge Oglala Sioux Tribal Council rescinded approval of the study in October 1991 as a result of concerns raised by residents of one reservation community. At the time the study ended, only one child had been vaccinated. During 1991, the epidemic of hepatitis A on the Pine Ridge reservation went on unabated with more than 500 cases and one death from hepatitis A.

In February 1991, the Standing Rock Sioux Tribal Council gave approval for the same study to be conducted on the Standing Rock reservation in North Dakota. Between then and the summer of 1991, extensive community education was undertaken through radio talk shows, newspaper articles, and information pamphlets. Participant recruitment began during the summer of 1991

and was conducted by three study nurses who were American Indians. As was the case in Pine Ridge, written informed consent was received from parents for their child's participation in the study; children 7 years and older also provided assent. A total of 245 children were enrolled in the study, 41 percent of whom were not American Indian.

In February 1992, the Standing Rock Tribal Council passed a resolution halting the study, although many parents wanted the study to continue. In March 1992, the tribal council decided that children who were already enrolled in the study could continue but no further enrollment could take place. However, the IHS and CDC decided that, given the interruption of the study and the limited number of children enrolled, a scientifically valid determination of the efficacy of the hepatitis A vaccine could no longer be made. Therefore, the study on the Standing Rock reservation ended and the codes were broken to reveal which vaccine was received by each child. For those who received hepatitis B vaccine, they were given the opportunity to receive the doses needed to complete the vaccination series. For those who had received hepatitis A vaccine, they were offered the complete hepatitis B vaccination series and informed they could receive the remaining doses in the hepatitis A series when a hepatitis A vaccine was licensed for commercial use. These children were offered the hepatitis A vaccine series when it was licensed in 1995.

On both reservations, the studies were stopped when the tribal councils withdrew their support. The tribal councils rescinded their approvals of the studies because a small group of citizens on each reservation raised concerns about the conduct of government research in the American Indian population. Among their concerns was that informed consent was not obtained. However,

in these studies the written consent forms identified the study as research, contained all the information about the vaccines and the study, and provided the parents with full disclosure. The consent forms were typed on stationary identifying the vaccine study as the Hepatitis A Vaccine Prevention Program and may have been perceived as a misrepresentation of the study to the participants. The use of the stationary was an oversight by the CDC and IHS investigators.

In 1995, the inactivated hepatitis A vaccine we attempted to evaluate in these studies was licensed for commercial use by FDA based on efficacy data obtained in a clinical trial conducted in Thailand. CDC's Advisory Committee on Immunization Practices (ACIP) currently recommends that children 2-14 years of age in American Indian or Alaska Native communities, or other communities with high rates of hepatitis A, be routinely vaccinated to prevent and control this disease. Currently, widespread hepatitis A immunization programs are being conducted in the IHS Aberdeen Area and in other American Indian and Alaska Native populations and have effectively interrupted and prevented community-wide epidemics in those areas.

Mr. Chairman, I would like to describe to you the importance of conducting vaccine-related research. Vaccines are the most powerful tools to prevent infectious diseases like measles and polio. The introduction of polio vaccine into the childhood immunization program has led to a reduction of wild virus induced disease from about 20,000 cases annually to zero in the United States. Widespread use of measles vaccine has decreased reported measles from more than 500,000 cases annually during the decade prior to vaccine availability to less than 1,000 cases per

year from 1993 to 1996 in the United States. Vaccines have led to the worldwide eradication of smallpox, and the elimination of polio from the Americas.

Currently, according to a CDC maintained database using manufacturer reports of net doses distributed, approximately 140 million doses of the most commonly used vaccines are distributed each year in the United States. These vaccines are used for both children and adults. The current immunization schedule calls for children to be protected against 10 diseases using 8 vaccines. Research is one of the best strategies to improve these products and develop new ones which are essential for the health and well-being of America's children and adults. Vaccine-related research has been an ongoing activity at CDC for many years and will continue to be a central focus; it is critical to preventing diseases and saving lives. While continuing this very important research endeavor, we will continue to work toward perfecting the informed consent process.

SUMMARY

I want to close by iterating several points. Good, ethical science is the foundation of sound public health practice. We cannot carry out our public health mission without the benefit of the knowledge gained through research and we cannot carry out research that does not protect the individuals or communities who participate. Assuring the rights and welfare of persons who participate in research is of paramount importance and the informed consent process is integral to assuring individuals' rights.

Concerns about the EZ measles vaccine study and the hepatitis A vaccine study have heightened sensitivity to issues surrounding the protection of human subjects. Moreover, these studies point to the important and significant role the community has in conducting research. We have made changes in our human subjects review process and will continue to make changes to achieve the best review process possible. We are also exploring ways to improve involvement of the community in the research process. Just as it is imperative to inform individual subjects, it is imperative to inform the community from which the subjects come and to encourage active participation of the community in the conduct of research. The quality of research is greatly enhanced by the community's participation and trust in the research.

CDC's goal is to ensure the fullest possible disclosure and the greatest possible protection from harm for persons and communities who participate in public health research studies. We are committed to building and maintaining the trust that is necessary between researchers and persons who participate in health studies.

I would be glad to respond to any questions that the Subcommittee may have.

Mr. SHAYS. I thank you. And we'll be happy to have you bring it up if we don't. Dr. Varmus.

Dr. VARMUS. Thank you, Mr. Chairman. I want to join my colleagues in thanking you and your colleagues for conducting a hearing on this most important topic. Let me briefly introduce the colleagues who came with me today—four institute directors who have serious concerns about issues and cases that your staff has brought to our attention: Dr. Duane Alexander, Director of the National Institute of Child Health and Human Development; Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases; Dr. Steve Hyman, Director of the National Institute of Mental Health; and Dr. Alan Leshner, Director of the National Institute on Drug Abuse. I'm also accompanied by Dr. Wendy Baldwin, my deputy director for extramural research, who has administrative oversight over the Office for Protection from Research Risks.

I'm going to talk briefly about protection of human subjects in research. I'll begin with a very brief description of our system for protecting research volunteers and then briefly speak to some of the initiatives we have underway to improve the system. A much longer statement describing these activities will be submitted for the record. The forerunners for the current system that you will be hearing about are the Nuremberg Code, which was developed to provide standards for judging human experimentation by the Nazis, and the Declaration of Helsinki, which was issued in 1964 by the World Medical Association.

These statements establish the principles of autonomy, beneficence and justice that underline many of the activities we'll be talking about. And as Dr. Satcher has just indicated, those principles are complex and sometimes even in opposition.

The NIH issued its policies for the protection of human subjects in 1966 and these were then established by the Department as regulations in May 1974.

Our regulations are not a set of rigid rules for determining whether research activity is right or wrong. Instead, they provide a framework for insuring that all serious efforts are made to protect the rights and the welfare of human research subjects. Responsibility for protection of human subjects is shared by a number of groups and institutions: the clinical investigator, the local institutional board—so-called IRB—in some cases a data and safety monitoring board, officials at the institutions that receive grants from the NIH and the CDC, as well as officials of the NIH. At each level of review, there is the authority to raise concerns about human subjects issues, to request further evaluation, and to suggest corrections of any identified problems. The Department's Office for Protection from Research Risks—the OPRR—while lodged administratively at NIH, exerts extensive oversight over the entire process involving a number of departmental agencies, especially providing oversight at those sites at which the research is carried out, often, for example, through assurances of compliance with our regulations.

A crucial part of the system is the requirement for informed consent, the topic of this hearing. The elements of informed consent are designed to ensure that before subjects enroll in a study, they

are fully informed about the study, about their rights regarding participation, and about the full range of risks and benefits of participation.

I want to speak briefly about the particular attention that needs to be paid to certain categories of research subjects. These are those people judged more likely than others to be vulnerable to coercion or undue influence to participate in a study. Our regulations contain specific protections for pregnant women, prisoners, children, and fetuses. And reviewers also are asked to pay particular attention to studies involving individuals with mental disabilities or reduced cognitive capacities, drug abusers and people who are economically or educationally disadvantaged.

Now, we believe the system we have created is generally effective, but it's not perfect. And occasionally, as you have heard, it seems to fail. For this reason we are continually working to enhance the system for protecting our subjects. I want to take a few final minutes to highlight a number of NIH activities that are aimed at making the system better. Many of these relate to the specific vulnerable populations I've just mentioned.

First, the NIH in collaboration with the Department of Energy and the Department of Veterans Affairs has jointly issued a request for applications for original research regarding "Informed Consent in Research Involving Human Participants." The goals are to test and develop alternative strategies that are relevant for diverse populations and to determine optimal ways to obtain informed consent. We have received more than 80 proposals at the time of the deadline for applications, and each of the three agencies has set aside funds in this fiscal year to support projects in response.

Second, six NIH institutes will soon cosponsor a workshop to develop principles to guide informed consent in the case of subjects who may be cognitively impaired. The cosponsoring institutions are the National Institute of Mental Health, the National Institute on Drug Abuse, the National Institute of Neurological Disorders and Stroke, the National Institute on Aging, the National Institute of Alcohol Abuse and Alcoholism, and the National Institute on Child Health and Human Development. Three of those institutes are represented here today. This workshop has been in the planning stage for some time, and we hope to have it by next fall.

Third, the advisory council of the National Institute on Drug Abuse recently has issued guidelines for research involving administration of drugs, especially drugs of misuse and abuse to human subjects. These guidelines for IRBs address the ethics of both human subject research in general and studies involving special populations. We've provided a copy of those guidelines to the subcommittee's staff. The National Institute of Mental Health—NIMH—has a number of additional activities underway. They have recently cosponsored a conference that addressed the specific ethical challenges involved in mental health research with children and adolescents.

In collaboration with the National Alliance for the Mentally Ill, the NIMH has cosponsored a series of meetings to discuss ethical issues of medical research involving human subjects with mental illnesses. In addition, the NIH and the Office for Protection from

Research Risks cosponsor annual regional workshops that focus on human subjects issues in mental health clinical research. The National Institute on Aging issued an announcement in the NIH Guide in October 1996 on implementation of policies for intervention studies, especially involving those subjects who may be mentally impaired.

And as one final item, the Clinical Center at the NIH, together with OPRR and several NIH institutes, has pioneered the concept of durable power of attorney applied to research participation. This procedure allows individuals, while they are mentally competent, to identify someone to represent their best interest and to provide proxy informed consent should they later become cognitively impaired.

Mr. Chairman, the people who volunteer to be research subjects are invaluable partners with us in the pursuit for new knowledge in medical science. Research investigators, research institutions, the NIH, and our partner agencies in the Department of Health and Human Services have a responsibility to protect those volunteers' rights and welfare. We take that responsibility very seriously. Thank you, Mr. Chairman. I'll be pleased to answer any questions you may have.

[Note.—The "OPRR Reports, NIH, PHS, HHS, Protection of Human Subjects" can be found in subcommittee files.]

[The prepared statement of Dr. Varmus follows:]

Mr. Chairman and Members of the Subcommittee:

I am Harold Varmus, Director of the National Institutes of Health. I am pleased to appear before the Subcommittee to describe our system of protection of human research subjects, a responsibility of enormous weight and critical importance. While the collection of scientific data to expand our knowledge of human ills is the ultimate aim of medical research, of equal importance is the protection of the individuals who assist us through their participation in research studies. Without these individuals, it would have been impossible for us to have made such remarkable progress in the development of effective treatment and prevention strategies for a host of human diseases and conditions.

History of Human Subjects Protection

May 30 marks the 23nd anniversary of the formal promulgation 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). This rigorous system of protections, designed to preclude the very problems we will discuss today, is guided by a set of principles--respect for persons, beneficence, and justice--which are the three quintessential requirements for the ethical conduct of research involving human subjects. It is based on a succession of judgments made by a variety of individuals in the context of DHHS regulations. Scientists, ethicists, lawyers, advocacy group members, and, most importantly, private citizens look at research protocols and weigh risks and potential benefits.

Let me take a moment to give you some background on the development of human subject protections. Our modern-day system began with the Nuremberg Code, which was developed for the Nuremberg Military Tribunal to provide standards by which to judge the human experimentation conducted by the Nazis. Many of the Code's principles regarding the ethical conduct of research involving human subjects still are followed today. It was followed in 1964 by the World Medical Association's *Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects*; and in 1966, NIH issued "Policies for the Protection of Human Subjects." which established the institutional review board (IRB) as one mechanism through which human subjects would be protected.

As I have mentioned, it was in May 1974 that the DHHS regulations were issued, elevating to regulatory status NIH's "Policies." Then in July 1974, the National Research Act was enacted, which established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The activities of the National Commission, which was active from 1974 to 1978, culminated in the development of the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.* The Report set forth the three basic ethical principles underlying the acceptable conduct of research involving human subjects, mentioned above, which continue to guide us today. Over the years, the DHHS regulations have been revised six times, adding additional protections for vulnerable populations.

Whose Responsibility Is The Protection of Human Subjects of Research?

Who is involved in protecting human subjects? The architecture of the current system involves at least half a dozen levels of protection. Ultimately, protection depends on several factors. First, the clinical investigator must be scientifically well-trained and also aware of his or her ethical responsibilities as a researcher, and committed to both the advancement of knowledge and the welfare of research participants. The initial planning of the research protocol is a vital part of the protection of human subjects, during which time the researchers perform a thorough review of the literature in order to develop a research plan and also to identify and articulate any potential risks associated with the research. The investigators must consider both benefits and risks associated with the research, build in safeguards for research participants, and formulate an extensive process to inform potential participants, to obtain informed consent for participation, and to document the consent.

Second, there is review and approval of the research protocol by a local IRB, a requirement of the DHHS regulations for Federally-supported research. Although non-Federal research is not covered by these regulations, you should be aware that the DHHS regulations are in general use by others as well. Many institutions voluntarily follow DHHS regulations for all their research. Following IRB review, additional review responsibilities rest with 1) the executive official of the research site; 2) the scientific review group at the NIH (generally, within the Division of Research Grants, or within an NIH Institute or Center [IC]); 3) the Advisory Council or Board of the funding IC; and 4) the executive official of the funding entity. Each has the authority to raise concerns about human subjects issues and to request further evaluation and correction of any problems found.

Once multiple review of the proposed study design and informed consent documents has been accomplished, and the proposal is funded, there is the crucial interaction between the research volunteer and the research investigator. It is at this point that the informed consent process begins -- when the research volunteer is apprised of what will be required for his/her participation in the study, including known associated risks. The informed consent document is only one component--the written component--of the informed consent process. I will describe the particulars of informed consent later. There also may be several individuals involved with the research volunteer during the process of obtaining informed consent, and throughout the course of the study, such as the nursing and scientific staff, as well as a physician. There also may be a consent auditor or monitor, or an advocate for the research subject to ensure that research subjects understand and are kept informed of any risks or proposed changes.

Role of the IRB

The role of the IRB is to protect the rights and safeguard the welfare of human research subjects. As I mentioned earlier, IRB review is required by DHHS regulations. The IRB must be established at the local level and have a minimum of five people, including at least one scientist, one nonscientist, and one person not otherwise affiliated with the institution conducting

the research study. Having the IRB at the research site is the cornerstone of our system of protection of human subjects. IRB review is a prospective and continuing review of the research by an impartial group of individuals, who are in the best position to know the resources of the institution, the capabilities and reputations of the investigators and staff, and the prevailing values and ethics of the community and, thus, the likely subject population. No federally-funded human subjects research may be initiated, and no ongoing federally-funded research may continue, in the absence of an IRB approval. The NIH cannot provide funds for human subjects research unless an IRB approves the protocol for such studies.

Once research is initiated that involves human subjects, IRBs have continuing responsibilities. These include the conduct of continuing review at intervals appropriate to the degree of risk, but not less than once per year; the authority to observe or have a third party observe the consent process and the research; prompt reporting 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; and 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.

Data and Safety Monitoring Boards

An additional layer of review that is sometimes employed is an independent Data and Safety Monitoring Board, or "DSMB," appointed to oversee and to evaluate the research investigation. Size and make-up of DSMBs vary; however, most include physicians with expertise in the disease under study, gained either through patient care or in the conduct of research, statisticians, and experts in scientific specialities. A patient advocate also may be included among the members of a DSMB. At periodic intervals during the course of a research study, the Data and Safety Monitoring Board reviews the accumulated data and makes recommendations on the continuation, or modification, of the study.

Institutional Officials

The final responsible party at the applicant/grantee institution is the institutional official, who signs-off on the research project when the application is submitted to the funding agency and assumes responsibility for the research project on behalf of the institution when the award is accepted.

Those directly involved with the protection of human subjects on behalf of the NIH are the members of peer review groups, the Director and other staff of the funding institute or center, and the Office for Protection from Research Risks (OPRR). Located administratively at the NIH, OPRR exerts extensive oversight of the entire process of human subject protection for HHS-supported research. Among its many responsibilities, the OPRR develops and monitors, as well as exercises compliance oversight relative to, DHHS regulations; establishes criteria and negotiates Assurances of Compliance with institutions engaged in DHHS-supported research

involving human subjects in research; conducts programs of clarification and guidance for both the Federal and non-Federal sectors with respect to the involvement of humans; and evaluates the effectiveness of DHHS policies and programs for the protection of human subjects. OPRR plays a major role in ensuring that human subjects of research are informed and protected and that thorough investigations of human subjects concerns are conducted. OPRR also investigates complaints from research subjects and others concerned with their welfare, and conducts a national program to educate the research community about human subject protections.

Members and staff of NIH scientific review groups and advisory councils evaluate the proposed involvement of human subjects in the research and identify questions, suggestions or concerns regarding protection of human subjects in the activity. These are communicated directly to the applicant before an award decision is made. If "concerns" are expressed by the review body, NIH program staff, with assistance from OPRR, work with the principal investigator and the institution to resolve any human subject "concerns" before a project is eligible for award. Grants management staff confirm that an applicable Assurance of Compliance and IRB approval have been obtained prior to award. Once these steps are completed, the Institute or Center Director makes the decision whether or not to fund the research project.

A Perfect System?

While I have emphasized the multiple layers of protection inherent in this system, I know you are most concerned about the possibility that this system can somehow fail. We acknowledge that despite our best efforts, there are occasions when the systems for protection are not perfect or the individuals charged with ensuring adequacy of these protections are unable to foresee potential problems--that is, there is always room for improvement in any system, including human subject protections. There have been research studies that have required further evaluation for human subjects concerns. To give you a sense of the kinds of problems we have encountered, I will relate brief accounts of selected research studies involving human subjects concerns and highlight actions taken to address them.

In one well-publicized instance, concern was raised about the proper explanation of research procedures and risks in the informed consent process for a study involving research subjects with schizophrenia at the University of California at Los Angeles (UCLA). After extensive OPRR review of concerns voiced, and of the institution's informed consent practices in general, it was determined that the IRB did not exercise sufficient oversight of the informed consent process. The institution was directed to revise the informed consent process. In addition, OPRR instituted close monitoring of the institution's human subjects activities, and issued a report on the investigation of UCLA activities relative to this protocol. As a result of this occurrence, the Acting Director of the National Institute of Mental Health (NIMH), the funding entity for the study, sent letters to over 200 clinical investigators to provide each with a copy of the OPRR report and to request that they carefully scrutinize all informed consent documents for full compliance with the OPRR recommendations. In 1995, the Institute released

a program announcement--Informed Consent in Clinical Mental Health Research--to expand upon previously funded research on informed consent. NIMH also has sponsored, and co-sponsored with advocacy groups, a number of workshops and conferences aimed at addressing issues specific to mental illness in clinical research.

In a second instance, concern was expressed about the misuse of an expedited IRB review process. OPRR identified failure of leadership within the IRB as the root of the problem, resulting in resignation of the IRB chairman. Sometimes, an OPRR review leads to a finding that the concerns were unfounded as in the case of another institution. OPRR followed up on concerns that were raised about whether a particular IRB was properly conducting the required annual review of continuing research. The institution demonstrated to OPRR that some 2,000 research protocols involving human subjects had, indeed, received continuing review by the IRB in accord with DHHS regulations.

Protection of Vulnerable Populations

Let me return briefly to the specific responsibilities of the IRB and the concerns IRBs must address. IRB review assures that risks are minimized; risks are reasonable in relation to anticipated benefits; selection of subjects is equitable; there is proper informed consent; and the rights and welfare of subjects are maintained in other ways, as well. This is particularly important when subjects are likely to be vulnerable to coercion or undue influence.

What populations are judged to be vulnerable? IRBs pay careful attention to research involving children, prisoners, pregnant women, individuals with mental disabilities, individuals who are economically disadvantaged, and individuals who are educationally disadvantaged.

The DHHS regulations provide extra protection for vulnerable subjects in several ways. If an IRB regularly reviews research that involves a vulnerable category of subjects, consideration must be given to including as IRB members one or more individuals who are knowledgeable about and experienced in working with the vulnerable population. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, IRBs must see that additional safeguards are included in the study protocol. Specific, detailed protections are actually written into DHHS regulations pertaining to pregnant women, fetuses, human ova fertilized in vitro, prisoners, and children. I would like to highlight some of the additional protections in place for several of these vulnerable groups.

Children

Recognizing the need for special attention to pediatric subjects of research, it is assumed that children are incapable of providing informed consent. As such, special protections are mandated for this vulnerable population. As required by regulation, parents or legal guardians must give proxy consent, termed "permission," for their children to participate in research protocols, and in most cases the children must agree ("assent") to their participation. In

protocols involving only minimal risk or those involving greater than minimal risk but which have the prospect of direct benefit to the child, only one parent must give permission. In protocols involving a minor increase above minimal risk or more than a minor increase above minimal risk in which the child stands not to benefit, both parents must sign a form giving their permission. Any research of greater risk and not intended to benefit the child can only be approved after review by a panel of experts and publication of the approval in the *Federal Register*.

As an additional protection--with specific, rare exceptions--children between the ages of 7 and 18 who are capable of understanding that they are involved in a research project are required to sign an "assent" form, which acknowledges their agreement to participate in a research protocol. Much care is given to writing assent forms in readily understandable language that is age-appropriate and to providing simple oral explanations, sometimes accompanied by visual demonstrations with dolls or by role-playing. Research investigators and nursing staff are often assisted in the "assent" process by patient advocates and assent auditors who are not involved in the research project in order to avoid any possibility of coercing the child into participating in the protocol.

Persons with Mental Illness or Dementia

Although there are no DHHS regulations providing specific protections for persons with mental illness or dementia, NIMH is giving special attention to informed consent issues related to their involvement in research studies. Recognizing the many issues surrounding patients with mental illness, the NIMH co-sponsored with the National Alliance for the Mentally Ill (NAMI) a series of meetings, including a symposium at the NAMI annual meeting, to discuss ethical issues concerning human subjects with mental illness in biomedical research. The NIMH and NAMI now are planning co-sponsorship of a meeting with a broader group of participants to develop a series of principles to guide informed consent with potentially cognitively impaired subjects. NIMH also sponsored a conference, *Ethical and Human Subjects Issues in Mental Health Research with Children and Adolescents*, to discuss the specific ethical challenges involved in this research. In addition, the NIMH and OPRR co-sponsor regional workshops to focus on human subject issues in clinical research with panels that specifically focus on mental health clinical research. These workshops, held throughout the country, are attended regularly by approximately 1,000 IRB members and researchers, annually.

Issues of informed consent are of particular concern for the elderly population, particularly with regard to Alzheimer's disease patients and others with diminished cognitive capacities. The National Institute on Aging (NIA) is participating in a Request for Application on informed consent in research involving human subjects, which I will discuss later. NIA is particularly interested in the role of cognitive function in aging, and the ability of the elderly to understand and remember so that information related to the consent process is meaningful.

In addition, the NIA issued an announcement in the NIH Guide to Grants and Contracts,

in October 1996 on "Implementation of Policies for Human Intervention Studies." This notice codifies additional oversight on the part of NIA Program Administrators to ensure the safety of participants in NIA-supported intervention studies.

Beyond these and the general NIH-wide guidelines on protection of human subjects, the NIA has no formal written guidelines for informed consent for research with Alzheimer's disease patients. However, efforts are being made to maintain consistent practices across large multi-site clinical studies. For the Alzheimer's Disease Cooperative Studies Program, the Principal Investigator reviews the consent forms from each site for consistency and appropriateness.

In addition, the NIH Warren Grant Magnuson Clinical Center--together with the OPRR, the NIMH, the NIA, the National Institute of Neurological Diseases and Stroke, and other NIH institutes--has pioneered the concept of the durable power of attorney applied to research participation, whereby individuals, while competent, could identify someone to represent their best interest and provide proxy informed consent should they later become cognitively impaired. The classic example of when this would be used is with participants in a study of progressive dementias.

Drug Abusers

The National Institute on Drug Abuse (NIDA) recognizes the importance of drug users (as well as other human subjects) to drug abuse research, and the special attention that must be given to ensuring informed consent in this special population. Therefore, NIDA and its National Advisory Council on Drug Abuse have developed recommended guidelines for the administration of drugs to human subjects, which address the ethics of human subject research in general and research involving special populations in particular. In addition to the roles that the IRB and OPRR play in ensuring the protection of participants in NIDA research studies, the Institute adheres to the basic principle and provides guidance that the investigator has the primary responsibility for the protection of vulnerable subjects. The investigator must give adequate consideration to the mental and physical conditions and motives of the individuals in terms of their ability to fully understand the context of the informed consent. If there is a question about a potential subject's ability to give meaningful and informed consent, an independent clinician, ethical consultant, or uninvolved third party with appropriate qualifications should be asked to evaluate this ability if the subject is to be entered or continued in the study.

Return to drug use is a key issue addiction treatment research, and relapse cannot be studied without the use of individuals who have taken drugs. Research that requires administration of drugs to individuals who are addicted to drugs warrant special attention, however. There are a number of extremely important issues that need to be addressed by scientists considering or evaluating requests to conduct research using drug-addicted individuals. Medical and neurological examinations and screenings must be made to ensure the absence of any medical or mental condition for which further drug exposure would be contraindicated. A thorough assessment of the risks entailed if the participant is to be exposed to a higher drug dose,

rate of administration, and/or new route of administration than they would normally use must be made. Finally and most importantly, investigators must make a serious and concerted effort to link these individuals to drug abuse treatment and other medical care.

The effects of drug use on adolescents is a major issue in drug abuse research and children are often involved in drug abuse prevention research. If the hypothesis being tested requires the involvement of individuals under age 18 and the benefit outweighs the potential risks, the investigator must: (1) obtain the individual's consent and/or assent to participate in the study; (2) obtain permission from the parent(s) or guardian for the individual to participate in the study; and (3) comply with any applicable local laws governing such research.

Assurance of Compliance With Human Subjects Regulations

The DHHS regulations for Protection of Human Subjects are not a set of rules that can be applied rigidly to make determinations of whether a proposed research activity is ethically "right" or "wrong." Rather, they are a framework in which investigators, IRB members, and others can ensure that serious efforts have been made to protect the rights and welfare of research subjects.

OPRR oversees implementation of the regulations in all DHHS facilities as well as domestic and foreign institutions or sites receiving DHHS funds. OPRR requires that each DHHS agency and extramural research institution that conducts research involving human subjects set iorth the procedures it will use to protect human subjects in a policy statement called an "Assurance of Compliance." An Assurance statement 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. The detailed, written Assurance statement becomes the instrument that OPRR uses to gauge an institution's compliance with human subject protections if there is a problem.

At OPRR's discretion, institutions with large research portfolios and demonstrated expertise in human subject protection may be granted a Multiple Project Assurance (MPA). An MPA, as the term implies, is an institution's pledge of full human subject protections for all federally-funded projects at the institution. More than 450 institutions currently hold an MPA. As an agency regulated by OPRR, the NIH Intramural Research Program, with 14 Institutional Review Boards overseeing research conducted at the NIH itself, has a Multiple Project Assurance from OPRR.

Informed Consent

All present today know how integral, and how crucial, the process of informed consent is to the protection of human subjects. Many have a general picture of informed consent, and it is

useful to add higher resolution to that picture. DHHS regulations specify 14 elements of informed consent. Of these, eight are required and are designed to ensure that research subjects are fully informed about the studies in which they are to enroll, the risks and benefits, if any, as well as their rights with regard to participation in DHHS-sponsored research. These are highlighted below.

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 that 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 that 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 will be paid, 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, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that 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 these elements of information in language understandable to the potential subject is not obtaining *informed* consent.

Implementing informed consent is a dynamic endeavor, and we are always seeking new perspectives. For example, a June 2, 1997, conference co-sponsored by the National Cancer Institute, the NIH Office of Research on Women's Health, the National Action Plan on Breast Cancer, and others, will seek to identify principles and models for prospectively obtaining, storing, and utilizing stored tissue specimens for research. Also, the National Bioethics Advisory

Commission (NBAC), which is charged with providing guidance to Federal agencies on the ethical conduct of current and future human biological and behavioral research, is reviewing all of the human subject protections for their adequacy and appropriateness today.

Special Considerations in Informed Consent

With any set of regulations, situations arise that require special consideration. DHHS regulations for Protection of Human Subjects do provide avenues for such occurrences, recognizing that certain consent procedures with IRB approval may not include or may alter some or all the elements of informed consent, or that a waiver of the informed consent requirement may be made. These avenues may only be used in certain narrow circumstances. The DHHS regulations (45 CFR 46.116(d)) provide for waiver of the requirements to obtain informed consent when all four of the following circumstances pertain:

- the research involves no more than minimal risk to the subjects; ("Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [45 CFR 46.102(i)].)
- the waiver, or alteration, of consent will not adversely affect the rights and welfare of the subjects;
- the research could not practicably be carried out without the waiver or alteration; and
- whenever appropriate, the subjects will be provided with additional pertinent information after participation.

IRBs are required to make and document these judgments.

Research on Informed Consent

Despite the specificity of Federal regulatory language on informed consent, its endurance through many years, and the enthusiasm with which we all adhere to it, there is little empirical work in existence to document the degree of understanding achieved by research participants. There is a paucity of data that bear upon, for example: 1) research subjects' comprehension of a study's methods and procedures; 2) subjects' understanding of relative risks and benefits of participation; 3) subjects' understanding of confidentiality and any exceptions to confidentiality; and 4) subjects' understanding of the implications of withdrawal from a study. Such data are needed to aid in designing informed consent procedures that are readily comprehended by prospective participants and, at the same time, impart all critical information.

In this vein, the NIH has joined with the Department of Energy and the Department of

Veterans' Affairs in a Request for Applications (RFA) for original research proposals in the area of "Informed Consent in Research Involving Human Participants." The sponsoring organizations are jointly issuing this RFA because voluntary informed consent is the defining aspect of interactions between researchers and participants, and is integral to the conduct of the scientific research funded by all of these organizations. One of the goals of this RFA is to bring together perspectives of these different agencies, since their different research foci reflect a diversity of issues relating to informed consent. Of course, many facets of understanding the informed consent process are shared, and hence a combined effort is efficient for the agencies and scientists alike. Such data should be useful in designing informed consent procedures that are readily comprehended by prospective participants and impart all critical information. The goal of the present initiative is to develop and test alternative strategies for obtaining informed consent in diverse populations and determine optimal ways to obtain informed consent for research participation.

The three agencies have set aside funds in FY 1997 to support projects in response to this RFA. More than 80 proposals were submitted by the March 11, 1997, closing date for receipt of applications. These three agencies are igniting the engine of research in an area that has for too long been under explored.

Conclusion

In the final analysis, Mr. Chairman and Members of the Subcommittee, research investigators, institutions, NIH, and DHHS are stewards of a trust agreement with the people who volunteer to be research subjects. We have a system in place that to the greatest degree possible 1) minimizes the potential for harm; 2) enables and protects individual, autonomous choice; and 3) promotes the pursuit of new knowledge. By doing so, we protect the rights and welfare of our fellow 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. I will be pleased to answer any questions you may have.

Mr. SHAYS. Thank you, Dr. Varmus. Thank you. And Ms. Pendergast.

Ms. PENDERGAST. Thank you, Mr. Chairman, members of the subcommittee. Good morning.

Mr. SHAYS. Good morning.

Ms. PENDERGAST. The Food and Drug Administration has put forward a longer written statement concerning the human subject protection system and the FDA's bio-research monitoring program. This morning I would like to briefly describe to you our regulations concerning research in life or death emergency situations.

Medical research is important. But the rights of human subjects in clinical trials are more important. Our attitude is grounded in the laws, in the ethical principles set forth in the post-World War II Nuremberg Code, in the Declaration of Helsinki, and above all in our conscious as individuals and as officials responsible for the protection of consumers and the public health.

We fully believe that medical research, which is intrinsically hazardous, must be conducted with complete integrity, that it must not be carried out at the expense of human subjects, and the their informed consent is the bedrock protection of their rights and self-interest. Therefore, when we had to consider the possibility of research without informed consent, we approached the task with great caution. We were asked to explore this option because new technology makes possible products that hold out the promise of saving lives in emergencies that were regarded as hopeless only a few years ago: lives of people who are close to death, cannot communicate, and require immediate treatment but whose condition has no proven remedy. To make this type of critical research possible while providing the maximum protection for the patient, we conducted extensive, indepth consultations with leading ethics, legal, research, patient advocacy, and minority communities.

With their assistance, and in cooperation with the National Institutes of Health, we issued in September 1995 a proposal that drew 16 negative comments, mostly from individuals who believed that informed consent should never be waived under any circumstances whatsoever. The other 74 commenters were strongly supportive. They included the National Stroke Association, the Brain Injury Consortium, the National Head Injury Foundation, the American Heart Association Emergency Cardiac Care Committee, the American College of Emergency Physicians, and the Applied Research Ethics National Association.

Our rule, Mr. Chairman, demands that informed consent be obtained whenever possible, but it also allows a waiver of informed consent in extremely limited emergency situations while safeguarding the subject's rights with overlapping layers of protection. The basic preconditions of the waiver are that the subject's life is threatened by an extremely serious condition, such as heart attack, stroke, or traumatic head injury; there is no proven or approved treatment; the intervention must be studied to determine what intervention is most beneficial; and informed consent of the subject or the legal representative is not feasible for several clearly defined reasons.

If all of these preconditions are met, the IRB—the Institutional Review Board—can waive the consent requirement in a particular

trial, but the subject's rights are protected in other ways. The IRB must find that the research holds out the possibility of direct benefit to the subjects. We call this clinical equipoise. The FDA must engage in a heightened review. We apply higher standards than usual to this research. There must be public disclosure of the proposed study to the community in which the research will take place. And the Institutional Review Board must consult with that community. The community must be engaged in the question of whether or not the research should go forward in their community. There must be public disclosure when the study is done. And there must be an independent safety and monitoring board. Finally, the researchers must continue to search out family members, next of kin, legal representatives, so that they or the person who, if the person becomes conscious, can be told about this study and asked whether they want to continue with it.

Mr. Chairman, these are merely the highlights of a complex system that is more fully described in my written statement. Let me close by assuring you that we and the many ethicists with whom we worked did our utmost to devise a system that exhaustively protects the subjects while saving their lives. The rules are too recent to pass any judgment on them. But we are committed to careful oversight of the rule's used. And we will modify the rule if needed. Thank you for your attention.

[The prepared statement of Ms. Pendergast follows:]

I. INTRODUCTION

Mr. Chairman and Members of the Subcommittee, good morning. I am Mary K. Pendergast, Deputy Commissioner and Senior Advisor to the Commissioner of Food and Drugs, U.S. Food and Drug Administration (FDA). I am pleased to be here today to discuss the Agency's policies with respect to the protection of human subjects in biomedical research. I will discuss the basic structure for human subject protection in the United States, the interconnection between FDA and Department of Health and Human Services (DHHS) regulations, and emerging issues in informed consent, including our exception to the informed consent requirements for those patient populations who are in need of immediate medical intervention but who are unable to give consent because of their medical condition. But first I will set out the protections the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the FDA's regulations afforded to research subjects, and the Agency's mechanisms to monitor and enforce those protections through Institutional Review Boards (IRBs), our Bioresearch Monitoring program, and educational efforts.

II. FDA'S STATUTORY AND REGULATORY BASIS FOR INFORMED CONSENT

The FD&C Act and its implementing regulations are one part of a complex system of safeguards that has been designed to promote the highest ethical principles described in the post-World War II Nuremberg Code, the World Medical Association's

Declaration of Helsinki, professional codes of ethics, and the reports and recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

In the system of safeguards that has evolved over the years, there are multiple levels of protection provided to research subjects. Each participant in a research effort -- the company that sponsors the research, the physician who conducts the research, and the IRB -- is obliged to protect the interests of the people who are taking part in the experiments. The FDA's responsibility is to see that the safeguards are met.

A. Responsibilities of the Research Sponsor

The sponsors of research -- usually, manufacturers or academic bodies, but sometimes individual physicians -- must select well-qualified clinical investigators, design scientifically-sound protocols, make sure that the research is properly conducted, and make certain that the clinical investigators conduct the research in compliance with informed consent and IRB regulations. The sponsor also has the obligation to make certain that any IRB reviewing one of its studies comports with FDA's IRB regulations. Sponsor obligations are set forth in the FDA's regulations that govern the design and conduct of clinical trials, and the requirements for submission of

applications to conduct clinical research (21 CFR Parts 312, 314, 601, 812, 814).

B. Responsibilities of the Researcher

The primary regulatory obligations of the clinical investigator are to: 1) follow the approved protocol or research plan; 2) obtain informed consent and ensure that the study is reviewed and approved by an IRB that is constituted and functioning according to FDA requirements; 3) maintain adequate and accurate records of study observations (including adverse reactions); and, 4) administer test articles only to subjects under the control of the investigator.

The essential core of FDA's informed consent regulations, 21 CFR Part 50, is that the clinical investigator must obtain the informed consent of a human subject or his/her legally authorized representative before any FDA-regulated research can be conducted. The researcher has to make sure that, whenever possible, the study participants fully understand the potential risks and benefits of the experiment before the experiment begins. The information provided must be in a language understandable to the subject, and should not require the subject to waive any legal rights or release those conducting the study from liability for negligence. Specifically, the clinical investigator must give the following information to

research subjects in seeking their informed consent to participate in research:

- A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- A description of any reasonably foreseeable risks or discomforts to the subject;
- A description of any benefits to the subject or to others which may reasonably be expected from the research;
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that FDA may inspect the records;
- For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained[1];

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[1]"Minimal risk" in both FDA and HHS regulations means that, "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of

- An explanation of whom to contact for answers to pertinent questions about research and research subject's rights, and whom to contact in the event of a research-related injury to the subject; and,
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. (21 CFR 50.25(a))

Depending on the nature of the research, other "additional" elements are required if they are appropriate to the research. These additional elements of informed consent include information about the anticipated circumstances under which the investigator may terminate the subject's participation, any additional costs to the subject that may result from participating in the research, the consequences of a subject's decision to withdraw from the study, a statement that the research may involve risks that are currently unforeseeable, a statement that significant new findings will be provided to the

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routine physical or psychological examinations or tests." (21 CFR 50.3(l), 56.102(i), and 45 CFR 46.102(i)) This definition is a key factor in the HHS regulations in its criteria for when informed consent may be waived. FDA and HHS published a list of categories of research in the 1981 Federal Register that could be reviewed by expedited means when they impart no greater than minimal risk.

subject, and the approximate number of subjects in the study. (21 CFR 50.25(b))

In short, the clinical investigator must tell the human subjects important information about the study and its potential consequences, so that the person can decide whether to be in the experiment. The entire informed consent process involves giving the subject all the information concerning the study that he or she would reasonably want to know; ensuring that the subject has comprehended this information; and finally, obtaining the subject's consent to participate. The process, to be meaningful, should involve an opportunity for both parties, the investigator and the subject, to exchange information and ask questions. It is up to the clinical researcher to make certain that, as best as possible, the person understands the information. To acknowledge that the person has received the information and has consented to the research, FDA also requires the clinical investigator to document in writing that consent was obtained. We recognize that the documentation of informed consent represents only one part of the entire consent process. The consent form itself is an aid to help ensure that a required minimum amount of information is provided to the subject and that the subject consents.

C. Responsibilities of Institutional Review Boards

An IRB is a group formally designated to review, approve the initiation of, and periodically review the progress of, biomedical research involving human subjects. The primary function of IRBs is to protect the rights and welfare of the people who are in clinical trials.

FDA's regulations, 21 CFR Part 56, contain the general standards for the composition, operation, and responsibility of an IRB that reviews clinical investigations submitted to FDA under sections 505(i), 507(d), and 520(g) of the FD&C Act. IRBs must scrutinize and approve each of the more than 3,000 clinical trials that are conducted on FDA-regulated products in this country each year. IRBs must develop and follow procedures for their initial and continuing review of the integrity of each trial. Among other requirements, IRBs must make sure that the risks to subjects are minimized and do not outweigh the anticipated study benefits, that the selection of participants is equitable, that there are adequate plans to monitor data gathered in the trial and provisions to protect the privacy of subjects and the confidentiality of data. The IRB has the authority to approve, modify, or disapprove a clinical trial. If an IRB decides to disapprove a research activity, it must notify, in writing, the investigator of its decision, state its reasons for the decision, and give the researcher an opportunity to respond in person or in writing.

The IRB must approve the informed consent form that will be used. If it finds 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 the research context, the IRB may waive the requirement that informed consent be documented. Where the documentation requirement is waived, however, the IRB may require the investigator to provide the research subjects with a written statement regarding the research. If the researchers fail to adhere to IRB requirements, the IRB has the authority and the responsibility to take appropriate steps, which may include termination of the trial.

An IRB must consist of at least five members with varying backgrounds to promote review of the covered research activities by persons of diverse disciplines. The IRB must have persons qualified in terms of professional experience and expertise. Considerations should be given to cultural, racial, and gender diversity, and sensitivity to such issues as community attitudes. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or physically or mentally disabled persons, the IRB must consider including one or more members primarily concerned with the welfare of those subjects. The IRB must include at least one member whose primary concerns are in scientific areas, one member whose primary concerns are in

non-scientific areas, and one member who is not otherwise affiliated with the institution (one person may fulfill multiple roles). 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.

The IRB is required to conduct continuing review of ongoing research at intervals appropriate to the degree of risk, but not less than once per year. It also has the authority to observe or have a third party observe the consent process and the research. IRBs are not required to register with FDA nor inform FDA when they begin reviewing studies.

III. HUMAN SUBJECT PROTECTION ACTIVITIES

FDA, which monitors the activities of research sponsors, researchers, IRBs and others involved in the trial, provides an additional layer of protection. We take no human right more seriously than the protection of people enrolled in clinical trials.

A. FDA's Bioresearch Monitoring Program

In order to protect the rights and welfare of human research subjects and to verify the quality and integrity of data submitted to FDA in support of marketing applications, FDA monitors all aspects of FDA-regulated research through a

comprehensive program of on-site inspections and data audits. FDA uses a combination of surveillance, enforcement, and education to achieve regulatory compliance. Under the Agency's Bioresearch Monitoring Program (BIMO), FDA field investigators and headquarters' scientists conduct site visits of research sponsors, clinical investigators, contract research organizations, IRBs, radioactive drug research committees, and non-clinical (animal) laboratories. In Fiscal Year 1996, FDA conducted approximately 1,070 inspections under the program.[2]

The BIMO program is implemented through several compliance programs: 1) Good Laboratory Practice (GLP) Program (Non-clinical Laboratory); 2) Clinical Investigator Program; 3) Institutional Review Board Program; 4) Sponsor, Contract Research Organization, and Monitoring Program; 5) In Vivo Bioequivalence Program; and, 6) Radioactive Drug Research Committee (RDRC) Program. The Clinical Investigator Program and the IRB Program are the primary programs for ensuring compliance with the informed consent requirements for human subjects in clinical trials.

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[2]Excludes color additives and radioactive drug research committee inspections, and includes domestic and foreign inspections.

FDA's Inspections of Clinical Investigators

Under the Clinical Investigator Program, FDA conducts study-specific inspections and audits of physicians and other investigators conducting clinical trials of FDA-regulated products. In Fiscal Year 1996 FDA conducted approximately 700 clinical investigator inspections.

FDA carries out two principal types of clinical investigator inspections: 1) study-oriented inspections; and 2) investigator-oriented inspections. Study-oriented inspections are conducted on studies that are important to product marketing applications, such as new drug applications (NDAs), product license applications (PLAs) for biological products, and premarket approval applications (PMAs) for medical devices, that are pending before the Agency.

The Agency routinely inspects and audits the pivotal studies upon which the Agency intends to base marketing approval of a new product. In these inspections and audits, FDA examines study records and findings, giving particular attention to protocol adherence and data integrity. We also look for documentation of informed consent and IRB review, approval, and continuing review of ongoing studies.

An investigator-oriented inspection may be initiated as a result of complaints received from subjects about alleged human

subject protection violations or when a study sponsor or FDA staff raise concerns about an investigator. If a clinical investigator fails in his or her obligations, FDA can reject the study, disqualify the clinical investigator from doing additional studies, impose certain restrictions on carrying out future clinical investigations, and in cases of fraud, pursue criminal prosecution. The names of clinical investigators who are disqualified or restricted are publicly available and can be accessed through FDA's home page on the World Wide Web. From 1993 through 1996, FDA disqualified four clinical investigators and imposed restrictions on the investigational drug use of six other clinical investigators.

FDA's Inspections of IRBs

The primary focus of FDA's IRB Program is the protection of the rights and welfare of research subjects, rather than validating the data obtained from research. FDA performs on-site inspections of IRBs that review research involving products that FDA regulates, including IRBs in academic institutions and hospitals as well as those independent from where the research will be conducted. All IRBs regardless of location or affiliation are required to conform to the same regulations and are inspected in accordance with the same compliance program. The inspectional data show that there are similar findings between types of IRBs. It has been demonstrated, however, that

IRBs being reinspected are more often found to be in compliance than those being inspected for the first time.

The frequency of the inspections depends on the performance of the IRB and the number of clinical studies it is monitoring. FDA's approach to these inspections traditionally has emphasized obtaining compliance through education, explanation of requirements, and cooperation but the potential for regulatory or administrative sanctions also is important.

The Agency has a very high standard for the quality of consent forms and applies this stringent standard during its inspections. We look to see whether the consent form includes all the information required by our regulations and whether there are areas in which the consent form could be improved, in our judgment. (We recognize that even a consent form that we find adequate, if submitted to other groups of persons, could be modified to "improve" it further -- so to at least some degree, the review of the adequacy of a consent form is subjective.) One of the reasons why we assign the review of consent documents to IRBs is because the IRB knows the most about its potential subject population and is best able to tailor the consent document to meet the information needs of that subject population.

The most common deficiencies that we find are: 1) lack of clarity about the person to contact if there are questions concerning the research and the research subject's rights in the event of a research related injury; 2) inadequate description of the research procedures to be followed; 3) inadequate description of available compensation if the subject sustains injury as a result of the research; 4) inadequate confidentiality statement; and, 5) inadequate description of alternative procedures that are available to subjects should they choose not to participate in the research.[3] A deficiency in the informed consent document does not necessarily mean that the informed consent process was inadequate. It is the interactive information exchange that is most important to the informed consent process. FDA focuses on the consent form during our inspections because it is the best evidence that we have of the basic information that was exchanged during that process.

FDA can impose administrative sanctions when necessary to protect human subjects of research and in cases of significant non-compliance. Significant non-compliance may include inadequate review of studies, inadequate record-keeping

[3] FDA recently published a final rule requiring informed consent documents to be dated at the time of signature (61 FR 57278, November 5, 1996). Although a common practice, this was not previously required by regulation. This new rule permits FDA to verify that consent was obtained prior to a subject's entry into a study.

practices that are so deficient that IRB review and approval cannot be verified, or not obtaining adequate informed consent from research subjects. FDA's sanctions include withholding approval of new studies that would be conducted at the institution or reviewed by the IRB, or directing that no new subjects be added to ongoing studies until corrections are made. In the most extreme cases of non-compliance, an IRB may be disqualified from serving as an IRB. Since 1993, approximately 59 warning letters have been issued and several consent agreements have been signed. To date, no IRBs have been formally disqualified by FDA, although several have ceased operations following FDA inspections. FDA also may ask the Department of Justice to initiate appropriate civil or criminal proceedings.

The following is an example of an administrative action FDA has taken with respect to an IRB for noncompliance with the Agency's IRB regulations.

In early 1994, FDA sent a warning letter to a major university, citing failure of the university and its IRB to protect adequately the rights and welfare of subjects in research. In this letter the Agency notified the IRB that it was no longer authorized to approve new studies, [under 21 CFR 56.120(b)(1)], and directed that no new patients be added to ongoing studies, [under 21 CFR 56.120(b)(2)].

The university was instructed to: (1) ensure that the IRB receives and acts on all reports of unexpected adverse events in order to protect adequately the rights and welfare of all research subjects; (2) ensure that the IRB and the principal investigators are informed of their mutual responsibilities for initial and continuing review of IND studies, especially the timely submission and review of all progress reports; and (3) ensure that the informed consent documents meet FDA requirements and that the clinical investigator only uses informed consent documents approved by the IRB.

In March 1994, FDA lifted its restrictions against the University after it agreed to correct the problems the Agency had found and documented the plan to accomplish this objective. At that time, FDA gave the university approval to again approve studies and add new patients to ongoing studies.

B. FDA's Review of Research Conducted Outside of the United States

FDA's protections extend beyond our national borders. All drug, biologic, and medical device studies conducted under an investigational new drug application (IND) or an investigational device application (IDE) are governed by FDA informed consent and IRB requirements. Regardless of the location of the research, our standard is the same.

In general, FDA also accepts foreign safety and efficacy studies that were not conducted under an IND or IDE provided that they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. We recognize that standards for protection of human subjects vary from country to country. If FDA, however, is to accept the data, the conduct of these studies must meet at least minimum standards for assuring human subject protection. Therefore, for studies submitted to FDA which were conducted outside the United States (and not under an IND or IDE), the Agency requires demonstration that such studies conformed with the ethical principles outlined in the Declaration of Helsinki or with the laws and regulations of the country in which the research is conducted, whichever provides greater protection of the human subjects.

Thus, as is evident from the foregoing discussion, there are many different entities which must be involved in the protection of human subjects. FDA works hard to make certain that all of the entities understand their roles and responsibilities and that they live up to the expectations placed on them. The protection of the people of this country who are willing to participate in medical research demands no less.

C. FDA's Educational Efforts

On our own and in cooperation with other professional and governmental organizations, we strive to inform those conducting and overseeing clinical research of how to meet their responsibilities and why their doing so effectively is important to protecting the rights and welfare of the human subjects who rely on them.

FDA has developed a set of over two dozen information sheets for IRBs and clinical investigators which address human subject protection issues -- including informed consent -- where questions or problems have arisen over the years. Each information sheet package includes the Belmont Report and the Declaration of Helsinki, important historical documents dealing with informed consent which might not be readily available to users, the FDA informed consent and IRB regulations, and a self-evaluation checklist for IRBs, cross-referenced to the regulations. FDA distributes the information sheets at professional conferences and meetings, through an automated facsimile system, and on FDA's home page on the World Wide Web. More than 6,000 copies have been sent directly to IRBs and to individuals who have requested them.

FDA staff frequently handle calls from IRB staff and members, clinical investigators, regulated industry representatives, and staff of other regulatory agencies on specific problem areas

and to give explanations of particular points in the regulations. When these contacts raise general issues, they are included in new information sheets. FDA also disseminates its educational message through articles and regular columns in professional journals. FDA's publications, including the Medical Bulletin (distributed to health professionals nationwide) and FDA Consumer, also include educational articles on human subject protection issues.

Professional conferences are an important arena for FDA's educational efforts. FDA recently held a one day national conference on human subject protection that was attended by over 500 people affiliated with IRBs, clinical research studies, and other Federal agencies. Additionally, FDA looks for opportunities to magnify the reach and effectiveness of its educational efforts by working with other organizations. For many years, FDA has cooperated with NIH's Office of Protection from Research Risks in a series of several educational conferences annually. The conferences are cosponsored by universities, medical schools, or other nonprofit institutions and are held in different parts of the country. A longstanding collaboration similarly exists with the premier professional organizations in the IRB field -- Public Responsibility in Medicine and Research and the Applied Research Ethics National Association. On a less regular basis, human subject protection education efforts are made at meetings of other health

professional groups and at meetings sponsored by non-profit organizations where sponsors make up a large proportion of the audience.

In addition to their inherent value in focusing attention on the importance of informed consent, FDA's educational efforts support our enforcement and product approval missions. Educated researchers who devote appropriate attention to informed consent and other human subject protections are likely to conduct studies of high quality in other respects as well. Such studies are easier for FDA to review and audit, and approvals can be issued more rapidly. The ultimate beneficiary is the American public, both those who participate as subjects in research and those who are treated with the products approved on the basis of that research.

IV. Interaction Between FDA and Departmental Regulations

Both FDA and the Department of Health and Human Services (HHS) have regulations pertaining to the protection of human subjects (21 Code of Federal Regulation (CFR) Parts 50 and 56 for FDA; 45 CFR Part 46 for HHS). The HHS regulations apply to research that is conducted or supported by HHS[4]; FDA's regulations apply to human subject research involving products regulated by FDA, whether privately or publicly funded. These FDA-regulated

[4]The implementation of these regulations is the responsibility of the National Institutes of Health (NIH).

products include, for example, investigational drugs, biologics, and medical devices. The FDA and HHS regulations are essentially identical, with differences only where required to reflect the distinct statutory mandate of the organizations and the focus of FDA regulations.

The two agencies apply the regulations in ways fitting their distinct missions. NIH implements the HHS regulations through assurances made by the institutions where the research is conducted. FDA regulates the investigators who conduct the research and the IRBs which review proposed research studies.

If a research project is conducted or supported by HHS and involves a product regulated by FDA, both sets of regulations will apply. In addition, most large research institutions receiving grant and contract support from HHS have agreed to review all research involving human subjects conducted at the institution in accordance with the HHS regulations regardless of the source of the funding for any particular study. The two sets of regulations are complementary and together they set forth criteria that are needed to protect research subjects.

FDA regulates clinical research of investigational drugs, biologics, antibiotics and medical devices under sections 505(i), 507(d) and 520(g) of the FD&C Act. FDA first imposed informed consent requirements on January 8, 1963, pursuant to

the 1962 amendments to the FD&C Act, which required that informed consent be obtained in most, but not all, research involving drugs. Later, in 1976, Congress imposed, through the Medical Device Amendments, an informed consent requirement for research involving medical devices, which was similar, but not identical, to the informed consent requirement for drugs. In 1981, FDA promulgated comprehensive informed consent regulations which applied the most recent statutory requirements to all FDA regulated research (21 CFR Part 50).

In 1981, FDA and HHS simultaneously promulgated new regulations establishing standards governing the composition, operation, and responsibilities of Institutional Review Boards (21 CFR Part 56, for FDA and 45 CFR Part 46, for HHS). These regulations established a common framework for the operations of IRBs that review research funded by HHS and research conducted under FDA regulatory requirements. In 1991, the "common rule" (modeled after the core provisions of the HHS regulations) was adopted by HHS, FDA and 14 other Federal departments and agencies that conducted, supported or regulated research involving human subjects. FDA modified its regulations to conform to the common rule to the extent permitted by its statutes. Last year, FDA published a draft guideline -- "Good Clinical Practice: Consolidated Guideline" under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of

Pharmaceuticals for Human Use (ICH). This guidance, while not a regulation, defines what is good clinical practice and provides a unified international standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

V. LIMITED EXCEPTIONS TO THE INFORMED CONSENT REQUIREMENTS

Having discussed the system for human subject protection, it is important to recognize that there are limited circumstances when informed consent is not obtained from a human subject or his or her representative. There are three "exceptions" to FDA's informed consent requirements. These exceptions are: 1) for a physician to preserve the life of an individual patient; 2) for the conduct of a narrow class of research in emergency settings; and 3) for use by the Department of Defense (DoD) of specific investigational products in combat exigencies.

The FD&C Act specifically requires that investigators inform subjects receiving drugs under an IND that the drugs (and biologics) are investigational and "obtain the consent of such human beings or their representatives, except where they deem it not feasible, or in their professional judgement, contrary to the best interests of such human beings" (Section 505 and 520). The Medical Device Amendments of 1976 provided that the sponsor of clinical investigations must "assure that informed

consent will be obtained from each human subject (or his representative). . . except where subject to such conditions as the Secretary may prescribe, the investigator conducting or supervising the proposed clinical testing of the device determines in writing that there exists a life-threatening situation involving the human subject. . . which necessitates the use of such device and it is not feasible to obtain informed consent from the subject and there is not sufficient time to obtain informed consent from the subject and there is not sufficient time to obtain such consent from his representative" (Section 520(g)(3)(D)). The three exceptions to the informed consent requirements that FDA has promulgated into regulation meet the standards described in those two statutory sections.

A. Preserving the Life of the Patient

According to the first exception (21 CFR 50.23 (a) and (b)) which has been in effect since 1981, informed consent of the subject or his/her legally authorized representative is required unless the investigator and a physician who is not otherwise participating in the clinical investigation, certify in writing, before the test article's use, that:

1. The subject is confronted by a life-threatening situation necessitating the test article's use.
2. Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain

legally effective consent from, the subject (for example, if the subject is unconscious). In contrast, a subject's inability to speak a particular language is not considered an inability to communicate.

3. Time is not sufficient to obtain consent from the subject's legal representative.
4. No alternative method of approved or generally recognized therapy provides an equal or greater likelihood of saving the subject's life.

The first three requirements are contained in the Medical Device Amendments. The fourth requirement was added by FDA to prevent routine reliance on the exception.

The regulatory requirement for this exception "applies to individual situations and not to categories of studies as a whole" (46 FR 8945, January 27, 1981), and suggests that there should be great confidence in the effectiveness of product, i.e., the situation must "necessitate" use of the product.

B. Conduct of Research in Emergency Settings

Because the section 50.23 exception was not formulated to apply to clinical trials, in October 1996 FDA promulgated a limited exception to the informed consent requirement to permit the conduct of a narrow class of research involving subjects in life-threatening situations (21 CFR 50.24). These regulations

set forth minimum standards designed to protect individuals who may benefit from emergency research (61 FR 51498, October 2, 1996). At the same time, the Secretary, HHS, announced a comparable waiver of informed consent requirements in certain emergency research subject to the HHS regulations (61 FR 51531, October 2, 1996).

FDA developed this second exception to the informed consent requirements following extensive consultation and deliberation with the ethics and research communities as to whether and how research could be ethically conducted in the acute care/emergency medicine context. In the summer of 1993, the Commissioner of Food and Drugs received letters from the neurology and emergency medicine communities expressing concern about their inability to conduct emergency research in subjects unable to provide informed consent because of conflicting HHS and FDA regulatory requirements. At a May 23, 1994, hearing of the Subcommittee on Regulation, Business Opportunities, and Technology, House Committee on Small Business, problems encountered in securing informed consent of subjects in clinical trials of investigational drugs and medical devices were discussed. At that hearing, Representative Wyden emphasized the need to harmonize the HHS and FDA regulations.

On October 25, 1994, professional and patient organizations and the bioethics community met at the Coalition Conference of

Acute Resuscitation and Critical Care Research to discuss this problem further. Following this conference, the Coalition developed a consensus document to resolve some of the issues concerning informed consent and waiver of consent in emergency research. The issue received further broad discussion at a meeting of the Applied Research Ethics National Association (Boston, MA, October 30, 1994) and at a conference sponsored by Public Responsibility in Medicine and Research (Boston, MA, November 1, 1994).

Concurrently and at the direction of HHS, FDA and NIH were working together to harmonize their respective informed consent regulations as they pertained to this emergency research. On January 9-10, 1995, FDA and NIH cosponsored a Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances in order to obtain as much public input from the research, legal, ethical, and patient advocacy communities as possible. FDA also sent "Dear Colleague" letters to the IRB community, called the major consumer and minority organizations which we thought would be interested in the proposed rule, and held briefings for the emergency research organizations as well as minority organizations in which questions about the rule could be addressed. It was only after all of these activities that FDA published its proposed rule on September 21, 1995 (60 FR 49086).

FDA received 90 comments in response to the proposed rule. The vast majority of these comments supported the proposal, although frequently the comments contained suggestions or requests for clarification. Of the 16 comments opposed to the proposed rule, the majority were from individuals who concluded that informed consent should not be waived under any circumstances. The comments were addressed in the preamble to the final rule published in October 1996.

The final rule provides access to potentially promising experimental treatments to patients in life-threatening situations. This rule sets forth special protections to human subjects who may benefit from this research, but who are not able to give consent on their own, and for whom a family member or legally authorized representative is not available to either withhold or give consent on the subject's behalf. Clearly, any researcher who can obtain informed consent must do so. Frequently, there are ways to design a study so that one is not confronted with emergency situations in which consent cannot be obtained. But in some cases, a subject cannot give his or her informed consent, for example, when there is a life-threatening emergency and there is no one available who is authorized to consent to an experimental treatment that might save that person's life. In that case, the Belmont Report directs us to

protect these individuals with diminished autonomy[5]. That is what the emergency research rule does. It recognizes the need for rigorously designed studies to obtain data on interventions in acutely life-threatening situations such as cardiac arrest and traumatic brain injury in those cases where existing therapies are either unsatisfactory or unproven and consent is not feasible. Without such studies, new therapies for critically injured patients may never be validated and patients in need of emergency medicine may never receive the benefit of improved treatments. Alternatively, such therapies could become widely used in the practice of medicine without any rigorous demonstration of their safety or effectiveness through clinical trials and emergency medicine physicians may never know whether they are in fact saving lives or harming patients through these interventions.

The emergency research regulation requires the following actions to be accomplished. Each study proposing to invoke

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[5]The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research stated in The Belmont Report that: "Respect for persons incorporates at least two basic ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy" (44 FR 23192, April 19, 1979). This report was in response to one of the National Commission's mandates, contained in the "National Research Act", P.L. 93-348 (See 42 U.S.C. 218). That mandate was to identify the basic ethical principles underlying clinical research.

this waiver must be submitted to FDA as a separate and clearly identified investigational device exemption (IDE) application or investigational new drug (IND) application. This will permit the Agency to very carefully review each of these studies to help ensure that they meet the narrow criteria of the rule before the study is allowed to proceed. The IRB and a physician free of conflict-of-interest must ensure each of the following for these emergency research activities to proceed:

- The human subjects are in a life-threatening situation;
- Available treatments are unproven or unsatisfactory; and
- Research is necessary to determine the safety and effectiveness of the particular intervention.
- It is not feasible to obtain informed consent from the subjects as a result of their medical condition or from the subjects' legally authorized representative because the intervention must be administered before they could feasibly be reached, and there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
- Participation in the research holds out the prospect of direct benefit to the subjects because: the life-threatening situation necessitates intervention; information from appropriate preclinical (animal) studies and related evidence support the potential for the intervention to be beneficial; and the risks associated with the research are reasonable in light of what is known

about the condition, the risks and the benefits of current therapy, and what is known about the risks and benefits of the proposed intervention.

- The research could not practicably be carried out without the waiver. That is, the research could not practicably be carried out in a subject population who could provide informed consent.
- The protocol must define the length of the potential therapeutic window based on scientific evidence and the researcher must commit to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking that representative for consent rather than proceeding without it. The researcher must summarize his or her efforts and make this information available to the IRB at the time of continuing review. The "therapeutic window" is the period of time in which the patient must receive the therapeutic intervention if it is to be effective.
- The IRB must have reviewed and approved informed consent procedures and an informed consent document consistent with FDA's informed consent provisions (21 CFR 50.25). These are to be used with subjects or their legally authorized representatives in situations where their use is feasible.
- The IRB also must review and approve procedures and information to be used when providing an opportunity for a

family member to object to a subject's participation in the research.

Additional protections of the rights and welfare of subjects are provided in this rule. These additional protections include:

- Consultation with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;
- Public disclosure to both of these communities prior to initiation of the research of plans for the research and its risks and expected benefits;
- Disclosure to the public of sufficient information following completion of the research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results; and
- Establishment of an independent data monitoring committee to exercise oversight of the research.

Because the default in this rule is that, once research has been approved by an IRB, eligible subjects are entered into these studies, the rule expands the number of caring individuals who may object to including a subject in one of these studies. Thus, if consent is not feasible from either the subject or a legally authorized representative, the

investigator must commit to attempting to contact within the therapeutic window, the subject's family member (who may not be a legally authorized representative) and asking whether he or she objects to the subject's participation in the research. The investigator's efforts to make this contact must be summarized and made available to the IRB at the time of continuing review.

The IRB also is responsible for ensuring that procedures are in place to inform each subject, legally authorized representative, or family member at the earliest feasible opportunity of the subject's inclusion in the research, the details of the research and other information contained in the consent document, and that they may discontinue further participation of the subject at any time without penalty or loss of benefits to which the subject is otherwise entitled.

These policies establish narrow limits for allowing research without informed consent in certain studies of emergency medical interventions, and harmonize these standards throughout HHS. We believe HHS's new overall approach to emergency research situations may offer the best hope, in an ethical manner, to critically ill, unconscious persons who have no readily available legal representative to give consent and who cannot be successfully treated through conventional means, but might benefit from a promising experimental intervention.

Since the promulgation of the final rule on emergency research, FDA has tracked all INDs and IDEs submitted under this rule. We have committed to an ongoing evaluation of the implementation of this rule to ensure its adequacy for protecting research subjects and to ensure it is appropriately applied. To date, there have been very few submissions under this rule. We have received one IDE application and four IND applications under the emergency research rule. This rule was designed, and is being used, only when it is not feasible to conduct research without a waiver. Thus, this rule is being used as it was designed -- only for that limited class of emergency research which cannot be conducted without a waiver and which meets the stringent criteria built into the rule to protect the research subjects.

This life-threatening situation rule was promulgated in response to growing concern that existing rules were making high quality acute care research activities difficult or impossible to carry out at a time when the need for such research is increasingly recognized. By permitting certain adequate and well-controlled clinical trials to occur that involve human subjects who are confronted by a life-threatening situation and who also are unable to give informed consent because of their medical condition, the Agency expects the clinical trials to allow individuals in these situations access to potentially life-saving therapies and to result in the

advancement in knowledge and improvement of those therapies used in emergency medical situations that currently have poor clinical outcome.

C. Department of Defense Combat Exigencies

The third exception to our informed consent requirements concerns the use of an investigational drug or biologic in certain situations related to military combat. During the months preceding the Persian Gulf War, DoD had discussions with FDA regarding the potential use of specific investigational products in military personnel serving in the Persian Gulf. We also had extensive internal discussions involving technical and policy-level staff, as well as experts from other Federal agencies and academia. It was thought that the products under discussion represented the best preventive measures for providing protection against possible attack with chemical or biological weapons. DoD requested the assistance of FDA in allowing the use of these products in certain battlefield or combat-related situations in which they considered obtaining informed consent "not feasible." FDA gave considerable deference to DoD's judgment and expertise regarding the feasibility of obtaining informed consent under battlefield conditions.

In response to this request, on December 21, 1990, FDA published an interim regulation amending its informed consent

regulations. This regulation allowed the Commissioner of FDA to determine, upon receipt of an appropriate application from DoD, that obtaining informed consent from military personnel for use of a specific investigational drug or biologic would not be feasible in certain circumstances, and to grant a waiver from the requirement for obtaining such consent.

The exemption extended, on a case-by-case basis, only to investigational drugs (including antibiotic and biological products, including those for protection against chemical and biological warfare agents) for use in a specific military operation involving combat or the immediate threat of combat. A request from DoD for an informed consent waiver must include the justification for the conclusion (made by physicians responsible for the medical care of the military personnel involved) that: 1) the use is required to facilitate the accomplishment of the military mission; 2) the use would preserve the health of the individuals and the safety of other personnel, without regard for any individual's preference for alternate treatment or no treatment; and, 3) the request contains documentation to indicate that the protocol has been reviewed and approved by a duly constituted IRB for the use of the investigational drug without informed consent.

Each application for waiver from the informed consent requirements was assessed by the appropriate FDA review

division, and by the Agency's Informed Consent Waiver Review Group (ICWRG). The ICWRG included senior management of the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Office of General Counsel, the Office of Health Affairs, and NIH's Office of Protection from Research Risks. The ICWRG core was supplemented by technical experts as appropriate for the particular investigational drug being considered for exception. The ICWRG considered DoD's justification supporting the request for the waiver and the reviewing division's evaluation of the available safety and efficacy data. The ICWRG requested additional supporting information in some cases, and required changes in the information to be provided to the troops in several rounds of iterative exchanges with DoD. The ICWRG then made a recommendation to the Commissioner regarding whether or not to grant the waiver. The Commissioner made a decision on the application and informed DoD in writing.

Under this regulation, waivers were granted for two products during Operation Desert Storm/Shield--pyridostigmine bromide and botulinum toxoid vaccine. Although FDA had concluded that informed consent was not feasible, FDA did obtain DoD's agreement to provide accurate, fair, and balanced information to those who would receive the investigational products. To do this, DoD developed information leaflets on both products with FDA's input and these leaflets received final FDA approval.

Following the cessation of combat activities, the Assistant Secretary of Defense for Health Affairs notified the Commissioner in a March 1991 letter that DoD considered the two waivers granted under the interim rule to be no longer in effect. He also informed the Commissioner that DoD had ultimately decided to administer the botulinum toxoid vaccine on a voluntary basis.

Since that time, the Presidential Advisory Committee on Gulf War Veterans' Illnesses has recommended that we "solicit timely public and expert comment on any rule that permits waiver of informed consent for use of investigational products in military exigencies." (Final Report, page 52.) FDA has carefully evaluated the committee's recommendations as well as other information that has come to its attention. FDA has engaged in discussions within the Agency, with DoD, and with others on this important topic. As a result of these discussions, the Agency will solicit public comment in line with the committee's report. This public comment will be directed towards whether the FDA should finalize the interim rule, modify it, or eliminate it completely.

VI. CONCLUSION

The first layer of the subjects' protection is provided by the medical research sponsor. It is the responsibility of the sponsor to design the research study to be ethically and

scientifically sound, select qualified researchers, provide them with the information they need to properly conduct the research study, and ensure proper monitoring of the study. The second layer of protection is provided by the researcher, whose professional and civic obligation is to conduct ethical research and make sure that the study participants are apprised of, and fully understand, the potential risks and benefits of the research. The third layer of protection is provided by IRBs. It is the responsibility of the IRBs to develop and follow procedures for initial and continuing review of the integrity of the research and the protection of the rights and welfare of its human subjects. The last layer of protection is provided by FDA, which regulates the organization and procedures of IRBs, researchers, research sponsors, and others involved in clinical trials. These layers of protections are applied to each clinical study to ensure the integrity of the data and in order to protect the rights and welfare of the human subjects of clinical research.

We take very seriously our obligation to protect the rights and welfare of all research subjects who participate in research involving FDA-regulated products. We believe that our regulations and inspection programs are important to help ensure that human research subjects are protected at the same time that vital information on the safety and effectiveness of drugs, biologics, antibiotics, and devices is gathered.

I would be happy to answer any questions you have about FDA's oversight and regulation of research activities.

Mr. SHAYS. Thank you. I think what I'd like to do is start with you, Ms. Pendergast. And what I would like you to do, if you don't mind, if you would read your statement and put it in the record orally beginning on page 37. I think that's where it begins. I'll tell you where. This relates to the Desert Storm issue. And if you could start with the second paragraph. And if you just read that paragraph, I'd like that on the record. And then I'd like to ask you questions about it.

Ms. PENDERGAST. The paragraph that begins "Under this regulation?"

Mr. SHAYS. Yes.

Ms. PENDERGAST. All right. We're referring now to a regulation that the FDA promulgated in December 1991 regarding waivers of informed consent during military combat situations.

Under this regulation, waivers were granted for two products during Operation Desert Storm/Desert Shield: pyridostigmine bromide and botulinum toxoid vaccine. Although FDA had concluded that informed consent was not feasible, FDA did obtain the Department of Defense's agreement to provide accurate, fair and balanced information to those who would receive the investigational products. To do this, the Department of Defense developed information leaflets on both products with FDA's inputs and these leaflets received final FDA approval.

Following the cessation of combat activities, the Assistant Secretary of Defense for Health Affairs notified the Commissioner in a March 1991 letter that the Department of Defense considered the two waivers granted under the interim rule to be no longer in effect. He also informed the Commissioner that the Department of Defense had ultimately decided to administer the botulinum toxoid vaccine on a voluntary basis.

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Mr. SHAYS. Let me ask you this to start my questions: Did the Department of Defense violate the conditions of the FDA's waiver of the informed consent requirement by not providing military personnel with information about the experimental drugs they were required to take?

Ms. PENDERGAST. As a condition of the waiver, we did negotiate an agreement with them where they would provide information sheets to the soldiers so that the soldiers, while not being allowed to decide whether they wanted to take the drug, they at least knew what they were taking, what it's risks were, what it's purported benefits would be. Unfortunately, we are advised by the Defense Department that they did not give all soldiers those information sheets.

Mr. SHAYS. So what is your answer to the question?

Ms. PENDERGAST. It's not clear to me that it's a violation of the regulation, but it is a violation of our agreement.

Mr. SHAYS. No. I asked is it a violation of the conditions of the FDA waiver. They didn't inform.

Ms. PENDERGAST. They didn't. No. There's no dispute about the facts, sir. I am only questioning because I have to look at the waiver document itself to ascertain whether that was in the waiver doc-

ument and one of the preconditions for the waiver. And I'm afraid I'd have to submit that for the record.

Mr. SHAYS. The war took place 7 years ago. Basically, 6 years ago. And you're telling me that the FDA still hasn't determined whether or not the Department of Defense was in violation of the notification requirement as a condition of waiving the informed consent?

Ms. PENDERGAST. No. I think that there's no dispute about the facts. We know that the information sheets were not provided to all of the soldiers.

Mr. SHAYS. OK.

Ms. PENDERGAST. You're asking me a different and more specific question.

Mr. SHAYS. Well, I don't think they were really provided to practically any of the soldiers. We've had eight hearings on the Gulf war. So this should show up on your radar screen. It's not something you need to check now. You need to make a determination of whether they were in violation or not. And I'm asking a question that it seemed to me that you could have responded 2 years ago. And so I'm going to repeat the question. Are they in violation of the agreement that the FDA had?

Ms. PENDERGAST. If you'll give me one moment, sir?

Mr. SHAYS. Sure.

Ms. PENDERGAST. The actual requirement that the information being given to the soldiers is not contained as a precondition in the actual written waiver document. So as a technical matter, it could be disputed that they were in violation of the waiver agreement. However, and more importantly from the soldiers' point of view and from our point of view, it was a promise that was not met.

Mr. SHAYS. So you're saying they promised to do it, but technically didn't sign an agreement to do it?

Ms. PENDERGAST. That's my understanding, sir.

Mr. SHAYS. What did they technically agree to?

Ms. PENDERGAST. There were a number of things that they agreed to do basically.

Mr. SHAYS. Not the promise, the technical.

Ms. PENDERGAST. No. The technical agreement. What it is, is we have regulations that describe the responsibilities of anyone who is conducting an investigation. And they basically go to the control of the drug, recordkeeping with respect to the administration of the drug, and recordkeeping pertaining to the adverse events or not of the administration of the drug. So there is a basic set of requirements. Because it was war, we recognized at the time that not all of the standard requirements would be capable of being met. This isn't administration in a hospital.

The pyridostigmine would have been given out in field combat situations. So what we did is we limited their requirements to a more limited set of requirements pertaining to information. If the worst possible thing happened and our troops were exposed to chemical or biological weapons then there were lots of obligations that kicked in, in terms of finding out what happened and whether or not the administration——

Mr. SHAYS. Ms. Pendergast, this is kind of painful here.

Ms. PENDERGAST. Yes.

Mr. SHAYS. The soldiers did take the PB pills. They did take them. They were under orders to take the pills. The Army was allowed to order them to take the pills because the FDA made a determination that the pyridostigmine bromide—the PB pills would be allowed to be used for a use that it had not yet been licensed for. You are telling me that the Department of Defense promised but did not sign an agreement that they would inform. Is it conceivable that they FDA would have allowed our soldiers to be required to take these pills without their being informed, at least that they may have a bad chemical reaction, that this was an experimental pill for this use? Is it conceivable the FDA would allow our soldiers to not be informed?

Ms. PENDERGAST. No, sir. As I indicated, we suggested and then worked with the Defense Department to create these information sheets so that the soldiers would have information——

Mr. SHAYS. They weren't informed. And you're telling me that they are technically not in violation of the consent because it was not a contracted, written agreement they promised to. But that was not part of the agreement technically. Was it part of the agreement technically that they would keep records?

Ms. PENDERGAST. Yes, it was.

Mr. SHAYS. OK. Did they keep records?

Ms. PENDERGAST. They kept some records. In our judgment they did not keep sufficient records.

Mr. SHAYS. So let me repeat my question. Were they in violation of the agreement?

Ms. PENDERGAST. In that sense, yes.

Mr. SHAYS. OK. So it terms of not informing our soldiers, they weren't in violation technically, but they were clearly in technical violation as well as in the spirit in terms of not keeping records of who was given these drugs and so on.

Ms. PENDERGAST. That is correct.

Mr. SHAYS. OK. So what is the Department doing about that? What is your agency doing about it?

Ms. PENDERGAST. Well, we've done a number of things. We have worked with the Defense Department to see if additional information could be provided to us. We have written them asking that if they have additional information on certain specific points that it be provided to us. In 1994, we sent them basically a "lessons learned" letter describing what was in our judgment the problems that we saw in the 1991 administration of the products and what could have been done better. And we are—as we indicate in our testimony—we are working to see whether or not this kind of a system worked and could work in the future differently or perhaps be abandoned.

Mr. SHAYS. So what I'm basically to infer from what you've said is, clearly the spirit of the law—for them to get this waiver of informed consent, the spirit of the law was they were at least to inform the soldiers that this was an experimental drug first and that the spirit of the law was clearly to keep records, but technically they were not required to inform the soldiers, which blows my mind. And you're saying technically they were required to keep records, which they didn't. And you sent out a letter in 1994 and

they have ignored your interaction and communication and you're satisfied?

Ms. PENDERGAST. Sir, we've never said we were satisfied. We recognize that this did not go well. We are, if anything, disappointed that it didn't go better.

Mr. SHAYS. No. Disappointed isn't good enough. Because this committee feels that some of our soldiers may have suffered severe physical problems as a result of taking an experimental drug in cases where maybe they took it after they were exposed to chemicals as opposed to before, and not knowing the relationship of when they should have taken these pills. So disappointed isn't good enough for us.

Ms. PENDERGAST. Let me explain. The law states quite clearly that informed consent may permissibly be waived if the obtaining of informed consent is not feasible or not in the best interest of the subject. That's our law. It was written in 1962.

Mr. SHAYS. Well, it was feasible. When they were given these pills, it was feasible to inform them. And that's the least they deserved.

Ms. PENDERGAST. At the time we wrote a regulation that addressed the question of whether or not informed consent was feasible in a military combat exigency, the testimony and the record at that time showed that the Defense Department indicated to us that during a military combat exigency, because of military command and in order to preserve the health and well-being, not just of the individual soldier, but of the other soldiers that would have to protect the soldier that had fallen as well as the troops as a whole, that informed consent was not feasible. The Food and Drug Administration accepted that representation.

Mr. SHAYS. I understand why they may have decided not to allow for soldiers to consent. I have no sympathy whatsoever they couldn't have informed the soldiers. And I am pained that after so many years have passed that you would concur in some way that they did not need to inform, that there was some military impossibility for informing.

Ms. PENDERGAST. Sir, I have not made that representation. The Defense Department has to answer the question as to why it was unable to give them the information sheets.

Mr. SHAYS. No. You have to enforce the requirements that they are technically required to. And have you enforced it?

Ms. PENDERGAST. Yes. I believe we have.

Mr. SHAYS. I wish you had just said "no" and we could have gone on. Because you haven't you have sent out a letter. There will be no response from the audience, please. You have basically said you have sent out a letter. You have basically accepted and put on the record that military activity prevented them from even living up to the technical requirements and certainly the spirit. And I want to know specifically now, given that you said you are enforcing this, I want to know specifically what you've done to enforce their failure to live with the spirit and the technical requirement that they agreed to.

Ms. PENDERGAST. As I indicated, we have expressed to the Defense Department in writing the problems we have found with their conduct of the administration of these drugs during Desert

Storm. And we have been working with the Defense Department and with others and the Presidential Commission on Gulf War Syndrome to ascertain what could be a better way of doing this.

Mr. SHAYS. You're talking about in the future. And I'm talking about the hundreds of thousands of soldiers who were sent into this conflict. And you have not told me how you have enforced their requirement. Have you asked for all their records?

Ms. PENDERGAST. Yes.

Mr. SHAYS. OK. How many have you received?

Ms. PENDERGAST. I can't tell you how many inches.

Mr. SHAYS. Pardon me?

Ms. PENDERGAST. I mean, we have received safety information and the other information that was required to be submitted under their investigational new drug exemption. As I indicated to you, it was not the type or quantity of information we would have hoped for——

Mr. SHAYS. That's an understatement.

Ms. PENDERGAST. We don't disagree with you. This was war. This was the first time. And it didn't work particularly well. We are in full agreement with you on that.

Mr. SHAYS. This isn't the first time the military has conducted themselves this way. And as long as they know the FDA is going to be a paper tiger with the military, they will continue to do this. They will continue to basically say "bug off." And as far as I'm concerned that's what they've said and that's what you've accepted. And you have said under oath that they have sent you information, you have asked for information. So it's just really important that you provide this subcommittee with specific requests and that you provide this subcommittee the results of what you requested. And we'll just continue this later.

I want to go on record as saying that I think this was an obvious question for me to ask you. I would have thought that you would have been very prepared to respond to it. And I think that if we didn't ask these questions after having eight hearings on this issue, that we would be derelict in our duty. And so we are going to pursue this with the FDA. Because in my judgment the FDA allowed the military to do what they have to do in time of war, to have gotten a waiver from informed consent.

They should have required that the troops technically, not just in spirit, be notified. And they should have made sure that it was being enforced. And the technical requirement of information, which is an outrage that it was not kept and data was not kept. And the FDA has not, in fact, really overseen this and sought to. And frankly, if you had said to me, we really blew it, just like the military, I could accept it. But you're defending it. So now we're going to pursue it. I have other questions for the other witnesses, but at this time I'm going to give Mr. Towns as much time as he'd like to consume.

Mr. TOWNS. I yield to my colleague from Ohio.

Mr. KUCINICH. Thank you very much, Mr. Towns, Mr. Chairman. I'm new to this subcommittee and to the Congress, but I have followed the Chair's tireless efforts to get to the bottom of the Gulf War Syndrome. And it's interesting to listen to this testimony, Mr. Chairman, with respect to the FDA's non-supervisory status. I

would like to ask the representative from the FDA, if she could answer this question? Since we've seen that the waiving of PB for military personnel in the Persian Gulf, waiving a consent for any reason can have serious consequences, do you agree that based on that experience there should be an immediate moratorium on waivers for any reason until some of the ethical problems that are being brought forward are addressed with comprehensive and stringent protocols for informed consent?

Ms. PENDERGAST. Yes; basically I agree with you. There are no waivers in effect at this time, and haven't been for a number of years. And the 1994 letter that we sent to the Defense Department was an indication that were there ever to be another waiver request considered—and there was no judgment made as to whether we would ever say yes again—but were we to even consider another waiver request, the specific standards would have to be much higher and more rigorous because of the failures.

Mr. KUCINICH. So you're saying this would never happen again? Is that what you're saying?

Ms. PENDERGAST. Not the way it happened this time. No.

Mr. KUCINICH. And do you feel that the Department of Defense ran roughshod over the FDA here?

Ms. PENDERGAST. It is difficult for us to say that. I think that the persons that we were dealing with were well-meaning. I also think that the FDA, which is an agency staffed with doctors and scientists, and not soldiers, has a very limited ability to second-guess what was going on in the Persian Gulf during the time of the war, and so——

Mr. KUCINICH. But when it comes to medical matters and matters related to bioethics, who should make the decision, a general or a doctor?

Ms. PENDERGAST. There is an obligation on the part of the Defense Department to have doctors in charge of making sure that the troops received the drugs properly and that the information was given to them, and that adverse events were reported back to the FDA. Doctors had to be in charge. That was part of the system that was in place as we went forward to permit the Defense Department to administer these products.

Mr. KUCINICH. So you're saying military doctors made the decision?

Ms. PENDERGAST. Military doctors.

Mr. KUCINICH. But are they subject to review by the FDA?

Ms. PENDERGAST. The military doctors basically had to report back to the FDA what they accomplished and what they failed to accomplish. And the reasons why the military doctors were able or unable to do particular things is a broader question of military logistics and chain of command during a theater of war. But from where we sat, we were talking to the military doctors who had obligations to do certain things and report back to the agency.

Mr. KUCINICH. You know, one of the things, if I may, and I'll let this go, Mr. Chairman, because I think that you've set the inquiry on a track that will eventually get the truth out, but something occurs to me about hearing this discussion. It's very disturbing, because the whole idea of consent—in a way, it's a matter of a time sequence. Troops are gathered to the Persian Gulf, they're put in

staging areas, they're engaged to the field. At some point along the way, even before people were sent out to the Persian Gulf, there was an understanding that they could run into an environment where nerve gas could be used. The idea of having PB came up, I'm sure, years before our troops went out there. And it just makes me wonder, Mr. Chairman, how this could have happened.

Because we're talking about a pick-up game, like a street basketball or street baseball game—everybody gets together and you make up the rules as you go along. People knew years before that if we were engaged in the Persian Gulf that nerve gas was a possibility. And for that reason it seemed to me that the exigencies of which we speak in combat are not a defensible argument for not providing informed consent. Because there was plenty of time to let anyone who would be in the Persian Gulf, Mr. Chairman—anyone who was going to be sent out there could have been told far in advance of being deployed to the field that they would be subject to taking a drug that could have certain consequences.

But the uniformed personnel never had that opportunity. And that's where I think the FDA has failed. And that's where, also, I think the Department of Defense failed our enlisted men and women. So I sat in a hearing which the chairman called, and we listened to men and women who are the victims of Persian Gulf Syndrome—they weren't told. So I have—I want you to know that I have a lot of respect for the role that the FDA plays in our society—I mean, to make sure that food and drugs that people consume are safe.

It's not a small matter. We all rely on it. It's like a basic trust that we have. But in order to rescue that trust, the FDA needs to come forward with a comprehensive statement of what went wrong and what you intend to do to make sure it will never happen again. Because it's very clear that there have been ethical breaches which undermine not only public trust but which have put human health on some kind of a foreign altar. And we ought never again be in a situation where this happens to our people.

Ms. PENDERGAST. May I respond?

Mr. KUCINICH. Please.

Ms. PENDERGAST. I think, Congressman Kucinich, you raise an incredibly important point. One of the things that we are looking at now is the question of, having accepted the fact that war may happen, is it possible to obtain basically anticipatory consent from troops? As in the question of, if you were ordered to take it, would you take it? And then only field the people into war zones who are willing to say or whatever. But that's a Defense Department question that I'm fully prepared—but that is the kind of debate that is going on.

I think if you go back and look at fall 1990, this issue first came up when the Defense Department was preparing for war. And I think in the view of hindsight we know that there may have been better ways of doing it. But at the time, they were trying to basically protect their troops. And I would like to say that these two products—pyridostigmine bromide and botulinum toxoid—are products that, although not approved for this use, had been widely and extensively used by people. Pyridostigmine bromide is approved and has been since the 1950's at doses 20 times higher than the

troops used. And people take it every day. And so we knew that it was a very safe product. Did we know it would work to protect them against nerve gas? No. Monkey trials showed it would. Did we know it would protect humans? No. But we had no way of knowing. Because it's not ethical to give somebody a prophylactic drug and then expose them to nerve gas and if you're wrong say, "Oh, I'm sorry." You just died. So you can't ethically test it. You do your best——

Mr. SHAYS. Excuse me. If the gentleman will——

Mr. TOWNS. It's my time. I'll yield.

Mr. SHAYS. If it's not ethical, then why did we do it to hundreds of thousands of our troops?

Ms. PENDERGAST. Because based on the information we had, it was indisputably safe and——

Mr. SHAYS. No. But you just made a comment.

Ms. PENDERGAST [continuing]. And we thought it was their best shot against nerve gas. You can't ethically expose someone to nerve gas as part of a clinical trial. That is the point where it's unethical. Nobody in the United States was ever going to expose our troops to nerve gas. The enemy was going to expose them. The question is what could we give our troops that would give them the best shot at making it through that adverse war time situation. We knew pyridostigmine bromide was safe. We had been giving it to people for 40 years. And we knew that in monkeys it had protected them against nerve gas. It was better than nothing. With respect to the botulinum——

Mr. SHAYS. Let me just say to you, if that's the logic you used, then apply it to the private sector as well. And you don't. I thank the gentleman for yielding.

Ms. PENDERGAST. With respect to the botulinum toxoid, that botulinum toxoid is used routinely by the scientists at the Centers for Disease Control and by other public health officials. Again, you can't ethically test biological and chemical weapons, even against volunteers. But that has been tested in animals. And it is used routinely by public health officials on themselves. Again, we though at the time that it was the best possible treatment or prophylaxis for our troops, that if we were going to war, if our children were going to war, we would want them to have that protection.

Mr. SHAYS. I'm sorry. If the gentleman——

Mr. TOWNS. I yield further.

Mr. SHAYS. No. I don't—I can even accept that you would ultimately have done that. I cannot accept for the life of me that you would not have required technically under law to have informed the soldiers. That I cannot accept. And I cannot accept once the war had ended, that the FDA wouldn't have been extraordinary vocal and active early on in making sure that records were kept. And if they weren't kept that they heard big time from the FDA in such a way that they would never even want to consider doing something like that in the future. And frankly, the response of the FDA, the anemic response of the FDA, tells me that the military knows they can be comfortable to do it again.

Mr. TOWNS. Let me move to another area, I think one even more basic. I'm concerned about the language used in some of these consent forms. It seems to me that you would have to be a person with

a Ph.D., almost to understand the content of these forms. I know that there is an effort to provide simple verbal explanation. However, I wonder whether you can provide a simple written explanation? So why don't I go to you, Ms. Pendergast, first, and then let others comment about it—because the consent form itself.

Ms. PENDERGAST. I'm not sure which consent form you're referring to. But it is one of the requirements of informed consent that it be written in a way that the subjects of the trial—the human volunteers—can understand it. So it has to be written—the regulations require that it be written in a way that the people who are receiving the information can understand it.

Mr. TOWNS. How do we arrive at that particular form? You see, have you seen some of those forms, those consent forms? I mean, all of them—that you find that, in terms of the way they're written, is just not clear. Just the average person would not be able to understand it.

Ms. PENDERGAST. The institutional review boards that must review research before it is allowed to go forward looked at——

Mr. TOWNS. That's another problem. Go ahead. I don't want to cut you off.

Ms. PENDERGAST. They're the ones that are closest to the community where the research is going to take place. So we look to them for that—their job is to protect the human subjects. And their job is to stand in the shoes of the volunteers to make sure that the volunteers are treated properly. And they are asked to look at those consent forms and make sure that those consent forms are appropriate for the people in their community who will be subject to the research. Whether they do it right all the time or not—I'm sure they don't. I'm sure mistakes are made. But if you look at the system, those are people who we turn to and say, is it in the right language, is it the right reading level, does it use too tough words, is it at the college level, should it be at the sixth grade or eighth grade reading level? Those are things that we turn to the institutional review boards to do.

Mr. TOWNS. But you know, I think maybe if you make your answers a little shorter you might not have as many problems.

Ms. PENDERGAST. Thank you.

Mr. TOWNS. Because what you're saying is, the review board—only CDC really—the review board—reflects the composition of the people that are going to be involved in the research. So why would you say—because that doesn't make a difference. Because if you have people that are involved in the review board that do not reflect the people that are going to be in the study, then what good does that do?

I don't understand how you're answering that. I can see CDC answering it that way, because there seems to be an effort to make certain that the people that are going to be in the study—actually that's the people that would be on the review board. Now, that's the only one I know—does anybody else?

Dr. VARMUS. That's true, also, Mr. Towns, of the review board that would review a proposal that's being carried out under the terms of an NIH grant. Virtually all of our grants go to academic institutions and research institutions which have review boards at the institutions composed of people who represent the community—

diverse with respect to gender and race. They are asked to interpret the consent form to be sure that it is understandable by the subjects. Now you're raising an important question, because if the language is too watered down you could argue that the study is not being adequately explained.

We work with these institutions through the Office for Protection from Research Risks to try to provide guidance. We've had tremendous experience at our OPRR, and we work with our institutions to be sure that they can find the happy medium.

Mr. TOWNS. Ms. Pendergast, can you say that?

Ms. PENDERGAST. Yes. The same rules are true for all the research that the FDA regulates. The review boards have to have gender and racial diversity. There have to be representatives from the community. And if the research involves children or other vulnerable populations, experts from those fields should be consulted.

Dr. SATCHER. Congressman Towns, let me——

Mr. TOWNS. Yes. Go ahead.

Dr. SATCHER. I just briefly want to say two things. I think the issue of informed consent is a very difficult issue. And I've been struggling with it for at least—well, going back to the sickle cell research center in Watts in the early 1970's, and I agree with Dr. Varmus. I think on the one hand, the critical issue is do people understand what you're saying. On the other hand, are you including enough content so that they really are able to explore the substance of what's going to go on with them. I think we just have to continue to struggle with this. I don't think we have perfect informed consent forms. Or IRBs, for that matter. I think we continue to make sure that the institutional review boards reflect the community. And it is a continuing struggle. Because sometimes you get people because you think they reflect their community and you find out later that they don't.

Mr. TOWNS. Right.

Dr. SATCHER. And then you put together an informed consent form, and then you find out sometimes the people don't read them. A lot of us do that. Not just people who have trouble reading. But a lot of us sign things without taking the time to read them. So we're struggling with all of those things. But what I think what we're trying to do is to improve communication between our institutions and the public that we're trying to serve.

Mr. TOWNS. Right. Dr. Raub, do you want to comment? Thank you very much, Dr. Satcher.

Mr. RAUB. I can add only in reinforcing my colleagues that the institutional review board is the first line of protection here. And every day they struggle with getting the message clear enough yet not so simplified that it misleads, and when they do explain a risk, explaining that risk in a way that is accurate without being so frightening or unnecessarily detailed as to mislead the subjects. There's been the constant struggle over the last several decades especially in a very litigious society where every time the risk is not disclosed adequately it then creates legal problems. So I think each board must struggle with getting the information as simple and clear as possible without being inaccurate or misleading or otherwise exploiting the individuals involved.

Mr. TOWNS. Right. Let me just sort of go back to something that was raised earlier. And I think that we have to be honest. I think that the chairman said something that I think that we need to really make certain that we put everything on the table. I'm concerned about the illusion of consents in certain circumstances. And of course, in the military or in prison, people are not free to say no. And I think we might as well go on and recognize this and admit it and let's move on. And I think that that's a fact.

And I think that, the chairman raising his question—also the gentleman from Ohio—that there is no need to dance around those kind of issues. There are certain situations and certain circumstances where people cannot say no, not in the true sense of no. We have to recognize that and then determine in terms of what we might try to do to begin to work on those kinds of things in order to make certain that people's rights are not violated. And I think that's an open and honest kind of discussion.

And I think that if we go about it any other way, I think that we're not really being fair to ourselves and the time that we're spending here together. So I want to lay that on the line, Ms. Pendergast, and to say to you that that's what we have to acknowledge. That's a fact. And of course—begin to deal with it. One more question, Mr. Chairman, and then I'm going to yield back, because I know that our time has been——

Mr. SHAYS. Mr. Kucinich will go after you. But you have more time.

Mr. TOWNS. OK. Fine. I'm concerned about the HIV trials being conducted in Africa, in the Caribbean and in Asia. There are allegations that these trials would have never been conducted in the United States. On the other hand, there are those who say that if these trials are halted, it would be difficult to conduct future drug trials in Third World countries. I would like each of you to comment on where we should strike the balance when considering drug trials in other countries.

Dr. SATCHER. Could I start? And the only reason I want to start is because that is the issue that I was referring to at the end of my testimony——

Mr. TOWNS. Yes.

Dr. SATCHER [continuing]. When I mentioned that sometimes there can be, if you will, what seem to be competing ethical principles. I think the AZT trials in Africa and Thailand and some of the other places throughout the world that are being carried out by NIH and CDC are funded in this country but also carried out by the World Health Organization and the United Nations AIDS program are an example of that in many ways. And recently a group, Public Citizen, raised some of those issues. And I want to say that it's a group that I respect.

And I agree with them on most of the issues. I disagree on this particular one. I believe the AZT trials that we're supporting and carrying out in Cote d'Ivoire and Thailand—and I'll just speak to those two for CDC—in fact do meet ethical principles. The debate is whether, in fact, they would be conducted that way in this country. As you know, the 076 trials were carried out primarily in this country and in France—well-developed countries. And they re-

ceived long-term, high dose AZT treatment to prevent the spread of HIV from mother to child, sometimes 16–24 weeks of therapy.

In the host countries where we're conducting those trials, there is no AZT treatment which is now standard in this country and in France and some other places. And the reason that there is no AZT treatment has to do with cost and complexity of the 076 regimen. The international community has never accepted the 076 regimen as appropriate for developing countries. So what we did in working with our host countries in Cote d'Ivoire and Thailand was to respond to their concerns about AZT, their desire to implement AZT, but their recognition that they couldn't do it the way we were doing it in this country.

Now, the two ethical principles—No. 1, there is an ethical principle about when you enroll people in a study: Do you ever give any group less than what is the accepted standard of care? In this case, the accepted standard of care in this country is not the accepted standard of care in those countries. The other ethical principle is, do you respect the host country? Do you answer the questions that the host countries have? Do you conduct studies that you are going to be able to implement the outcome after the studies are over?

And we have decided that in order to make a difference in those countries and to save lives we need to have the kind of studies in which we have a placebo control versus short-term AZT, like 3 to 4 weeks, as opposed to the 16 to 24 weeks. And therefore, our studies are looking at: Can we make a difference using short-term AZT therapy that costs about $50 as compared to $800 to $1,000 for the 076 approach that we use in this country, in countries where the average expenditures for health are $10 per capita. Those are the issues, I think, in the AZT trials. And that's why they're done differently. And those are the debates. I hope I've captured the essence of——

Mr. TOWNS. You have, but there are still some problems that I have. It is my understanding that when you have this going on, that the doctor who's in charge of it is also responsible for the overall medical supervision for the patient. I'm not sure that's safe. If I'm involved in research and I see a certain type of behavior that I think that somebody else should be able to evaluate and determine whether it should be continued or stopped.

Dr. SATCHER. Right.

Mr. TOWNS. I have so much invested in it as a person who's providing the research, that I won't stop even though I see signs that——

Dr. SATCHER. Exactly. I think it's a very important point. These studies had to be approved by the CDC institutional review boards before they were funded. They also had to be approved by the host countries' review boards, in Cote d'Ivoire and in Thailand. They have an oversight board. Not the physicians treating the patients, but a board of people constituted to look at the proposed studies and to answer the question: Are they appropriate for this population? The rules also say that they are to revisit those studies periodically and say, "Has anything changed in terms of benefits and risks? If so, then should we continue these studies?"

One of the studies in Cote d'Ivoire, for example, we observed very early that there is a 10 percent still-birth rate among participants

in the study. It turns out that whether people were receiving AZT or the placebo, they all—in that country there is a 10 percent rate of still-births among women who have HIV infection. So if we did not have the placebo group, we would not have known that. We obviously would have thought that it was the AZT that was causing the still-births. So I think the studies are organized in such a way and the oversight is done in such a way as to protect against the concern which you have. And I think it's a valid concern. I think if we relied on the people who were just treating the patients to carry out these studies, I think you're absolutely right. It would violate the rights of the patient.

Mr. TOWNS. Any other comments? Yes?

Dr. VARMUS. Mr. Towns, may I just comment briefly? I agree with many of the comments made by my colleague, Dr. Satcher. The issues that were raised by Public Citizen and that have been brought to your attention are not new ones. The 076 trials that demonstrated the efficacy of AZT in preventing maternal to infant transmission in this country and France were brought to conclusion. The World Health Organization organized a meeting in Geneva to consider the implications of those studies for the developing parts of the world where the transmission rate is, in fact, at its highest.

It was generally agreed that in thinking about how we could translate the success of 076 to the other parts of the world where transmission was so frequent, we had to confront what is an evident fact to anyone who travels in many parts of the world: Namely what we in Europe and North America and other places receive from advanced medicine simply is not available nor affordable in those countries. The 076 trial was a very complex trial, and the methodology was very expensive and sophisticated.

It was generally agreed by representatives of both developing and developed countries that any effort to carry out studies that would be effective and feasible in the developing world would have to involve studies that actually could be used. In fact, one injustice that could be perpetrated upon those countries would be to go there and do studies that were only applicable in parts of the world that could afford the therapies.

There are many examples of that principle. It is one that is uncomfortable, because all of us would like to feel that the advanced medicine that is available to us could be available to all. But it's a fact of life that it's not. There are simple, cheap therapies that do work. A classical example is, as the trial carried out some years ago in Bangladesh, to ask whether oral hydration therapy for patients with cholera would work when we knew that in this part of the world intravenous hydration is effective. Well, intravenous hydration would not be a very feasible therapy in small villages.

Oral rehydration works. It turns out, when the trial was done it was extremely beneficial. That's a good example of why doing the appropriate trial can be of immense benefit. These are complex issues. We believe that the trials being carried out, which have been subjected to many review processes that Dr. Satcher has alluded to, have satisfied all the criteria for responsible review.

Mr. TOWNS. Dr. Raub.

Mr. RAUB. I don't believe I need to add any further detail to that. I share the basic principles that Dr. Satcher and Dr. Varmus have enunciated.

Mr. TOWNS. Thank you.

Dr. VARMUS. Mr. Towns, I would be pleased to provide for the record, if you would like, some letters that we have received from institutions both in African countries and in this country that are carrying out the collaborative work, who have responded to the letter from Public Citizen. I think you would find them reassuring. And I would be pleased to provide them for you, if you'd like.

Dr. SATCHER. I just want to add one thing because I think there is another critical issue here. I don't know all of the history behind some of the studies that have gone on, but I have visited Cote d'Ivoire and I know the people there and have worked with the people there in terms of what they really want to achieve from these studies. I know their concern about not being able to use AZT. I've met with the Minister of Health and the U.S. Ambassador there.

We have funded the virology laboratory there. We are training people who in the future will be able to conduct studies like this and even more sophisticated ones in their own countries. I don't want you to think that this is just a study that we're going in, doing a study and coming out. Our commitment in these countries is to develop the kind of relationship that they will be able to buildupon. I think that's happening.

Certainly in Cote d'Ivoire. And I think it's happening in Thailand. I'm going to visit there in July. But I think what we're trying to do is to develop relationships that will be supportive and ongoing. And they're doing the same thing. They're visiting us, and in many cases contributing to what we're trying to do in very useful ways.

Mr. TOWNS. Mr. Chairman, I have a letter I'd like to add to the record, which is the subject of Public Citizen's news release. And it says—it's actually a letter to Dr. Varmus. And I'd like to include in the record—from Uganda Cancer Institute. So I'd like to make it a part of the record, as well. And it talks about, "I read with dismay and disbelief the above-mentioned documents regarding clinical trials in developing countries with special emphasis on those taking place in Uganda." So I'd like to make this a part of the record.

Mr. SHAYS. OK.

[The letters referred to follows:]

Insert for the Record of the May 8, 1997, Hearing before the House Government Reform and Oversight Subcommittee on Human Resources, page 78, lines 1771-1777.

Letters from US/Africa Addressing *Public Citizens* Criticisms of the AZT Trials in Developing Countries--Offered to Representative Towns for the hearing record by Dr. Harold Varmus, Director, National Institutes of Health

- May 4, 1997, from Richard Semba, M.D., Johns Hopkins University /the Wilmer Ophthalmological Institute
- May 5, 1997, Maria J. Wawer, MD, Columbia University School of Public Health, Center for Population and Family Health
- May 6, 1997, from Neil Halsey, et al., Johns Hopkins University School of Hygiene and Public Health, includes
- May 6, 1997, from Christopher Whalen, MD, et al., Case Western Reserve University, Uganda-CWRU Research Collaboration (includes Journal of Law, Medicine and Ethics article on *Research Bioethics in the Ugandan Context: A Program Summary*
- May 7, 1997, from Wafaie W. Fawzi, et al., Harvard University School of Public Health
- May 7, 1997, from Andrea J. Ruff, MD, Johns Hopkins School of Hygiene and Public Health
- May 8, 1997, from Edward K. Mbidde, Uganda Cancer Institute
- May 8, 1997, from Greg Hussey, Dept. Of Paediatrics and Child Health, University of Cape Town

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4 May 1997

Dr. Harold Varmus
Director
National Institutes of Health
Bethesda, Maryland
United States of America

Dear Dr. Varmus:

As you are aware, we are conducting a NIH-sponsored clinical trial to evaluate vitamin A supplementation for HIV-infected women in Malawi, a country in south-central Africa. The rationale for conducting this clinical trial was that our previous studies in the same location showed that low maternal vitamin A levels were associated with increased mother-to-child transmission of HIV, low birthweight, increased infant mortality, and child growth failure. As these were epidemiological associations, it was unknown whether giving supplemental vitamin A might improve the health of HIV-infected mothers and their infants. Related studies are also in progress in other countries.

The goals of the study are to determine whether vitamin A supplementation during pregnancy in HIV-infected women will reduce mother-to-child transmission of HIV, increase birthweight, reduce infant mortality and/or reduce growth failure of children. If the study should show benefit for any of these child health outcomes, vitamin A supplementation may be an appropriate and affordable strategy (at about US 35¢/person) for the country of Malawi to improve child health. In Malawi, 20% of infants are of low birthweight, and 14% of infants die before one year of age, the seventh highest infant mortality rate in the world.

Malawi is one of the poorest countries in the world, with a mean per capita income of US $ 210 per year. The per capita health expenditure is less than US $ 5 per year. Anti-retroviral therapy, such as AZT, is unavailable in the entire country, and if it were, it certainly could not be afforded by most of the population. During the last few years,

Queen Elizabeth Central Hospital, the teaching hospital of the University of Malawi and the largest in the country, has often had no antibiotics at all, no sterile gloves, and no working x-ray machine. Hospital linens are often unavailable and the sterilization equipment frequently breaks down. The physicians and nurses are working under tremendous pressures and difficult circumstances to provide basic medical care in the face of a growing AIDS epidemic. Medical care is on the level of oral rehydration therapy, vitamin A capsules for measles, and basic immunizations. Resources are stretched to their limit, and the people are looking for affordable, appropriate, and sustainable long term strategies to improve health.

The Johns Hopkins University began their commitment towards assisting the people of Malawi in the fight against the AIDS epidemic with NIH-sponsored collaboration in 1988. The collaboration built up infrastructure, research, and training which were instrumental in the epidemiologic characterization of the AIDS epidemic in Malawi. Under the collaboration, many Malawian health care professionals received training at Johns Hopkins University (1 PhD degree, 5 MPH degrees, and 25 with advanced training in laboratory sciences and epidemiology). In addition, visiting faculty from Johns Hopkins University have provided in-country training in epidemiology and infectious diseases for over 100 Malawian health care professionals. The Johns Hopkins/University of Malawi collaboration has been a very successful model for international collaboration and development. Johns Hopkins faculty have maintained a continual presence on-site in Malawi, beginning with Drs. Paolo Miotti and Gina Dallabetta, Dr. Taha E. Taha, and now Dr. Newton Kumwenda.

Our colleagues at the College of Medicine at the University of Malawi were fully in agreement that a vitamin A supplementation trial should be undertaken in Malawi. We have not undertaken a study involving a full course regimen of AZT (such as the ACTG 076 protocol) in Malawi because of concern in the country that it would be unethical to undertake such studies involving AZT in Malawi because nobody in Malawi could possibly afford AZT. Physicians in Malawi have told us on occasion: "Don't use us as guinea pigs for drugs you are using in the United States of America that we cannot afford to use here." The use of AZT in the context of a vitamin A supplementation trial in Malawi would have made the results of the study useless to the people of Malawi, the very people who we are trying to assist.

A full course of AZT to prevent mother-to-child transmission of AZT costs about U.S. $800-1000/person, which is not a long term solution for Malawians. We do not wish to practice what has been called "helicopter medicine" – in which unaffordable and unsustainable therapies are given for a short period of time in developing countries -- and then withdraw these therapies and fly off into the night, leaving the people to their crushing poverty. Such an approach provides no long term solutions for the people in Malawi. It violates basic ethical principles of international development, namely, appropriate technology transfer and sustainable development.

We have a long term commitment to the health of the people in Malawi in finding constructive and appropriate solutions to HIV treatment and prevention

Yours sincerely,

Richard D. Semba, M.D., M.P.H.
Assistant Professor of Ophthalmology, Molecular Microbiology and Immunology, and Human Nutrition, International Health

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Center for Population and Family Health
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May 5, 1997

Dr. H. Varmus,
Director,
National Institutes of Health.
Bethesda, MD

Dear Dr. Varmus:

I am writing in regards to concerns recently raised by Public Citizen with respect to US Government sponsored research in developing countries. I am the Principal Investigator of the Rakai STD Control for AIDS Prevention Project (RO1 AI 34826) and the Maternal Infant Supplementary Study, large community-based randomized trials being conducted in rural Uganda to assess the effectiveness of intensive STD control as a means of reducing HIV transmission and acquisition. These studies represent applied, policy oriented research with the goal of developing cost effective and feasible methods of HIV and STD control appropriate to developing countries. The trials represent a joint research collaboration between the Ugandan Ministry of Health/Uganda Virus Research Institute, Columbia University and Johns Hopkins University.

Although the Rakai Project was not among the projects singled out by Public Citizen, I believe it is important that both US and host country researchers work together to address the issues raised by Public Citizen. As a researcher actually working overseas, I would like to stress that such studies represent very close collaboration between host country institutions, researchers and local communities, and the US-based scientists. The Rakai Project is the result of an extensive and detailed collaborative planning and monitoring process conducted from the community level on up to the Ministry of Health in Uganda, and continues to undergo thorough evaluation by appropriate Ugandan ethical and scientific oversight committees, including the AIDS Research Subcommittee of the Ugandan Council for Research and Technology. In the Rakai Project, as in other international studies, great effort is devoted to the selection of treatment and control arm activities, in order to appropriately test interventions which can be replicated and can have direct benefits for host country residents. My colleagues and direct counterparts in Uganda (who include the Ugandan Co-PI Dr. N.K. Sewankambo, Associate Dean of Medicine at Makerere University, and Dr. F. Wabwire-Mangen, Director of the Institute of Public Health) are highly experienced researchers for whom long term benefits to Uganda represent a major goal of any in-country research.

As is the case within the Rakai project, host country researchers and policy makers must continue to have the final say regarding the interventions to be tested; comparing such interventions to prevailing standards of care represents the one means of determining whether a treatment or prevention strategy will be beneficial within the context of a given developing country. Comparing feasible interventions to standards of care available to (in many cases only a minority of) US citizens, will have the negative effect of depriving host countries the opportunity to adequately test and subsequently implement strategies which could actually benefit many more of their residents.

Thank you for this opportunity to contribute to the current discussion,

Sincerely yours,

Maria J. Wawer, MD
Associate (Clinical) Professor
PI, Rakai Project

cc. Dr. Mary Glen Fowler
Dr. Mark Grabowsky
Dr. Rod Hoff

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Division of Disease Control

May 6, 1997

Harold Varmus, MD
Director
NIH
Office of the Director
Building 1, Room 126
Bethesda, Maryland 20852

Subject: Public Citizen criticism of clinical trials to evaluate interventions to prevent maternal-infant HIV transmission.

Dear Dr. Varmus,

As faculty of the Johns Hopkins University who have participated in efforts to improve the health of children in developing countries, we are concerned about the issues raised by Public Citizen and we want to provide you with our perspective on this issue. Many of us have been deeply involved in trying to control the HIV pandemic for more than 12 years. We have seen the impact of HIV on families throughout the world and we have participated in the usually hopeless efforts to provide care for HIV infected children and their parents in developing countries. Everyone involved, including Public Citizen, wants to prevent these infections. However, the proposal of Public Citizen to stop or alter the ongoing and planned studies would lead to a delay in bringing potentially effective interventions to developing countries. This would result in the needless death of hundreds of thousands of children. Each year more than 300,000 babies in developing countries are infected with HIV. For every month we delay in finding an effective simple intervention that can be implemented in developing countries, more than 20,000 children die from HIV infection. Also, the Public Citizen proposal would set a precedent that could prevent the United States from assisting poor countries to find other practical, affordable and effective interventions for prevention or treatment of other diseases.

In the 1980's and early 1990's we worked with developing country

investigators to document the extent of the HIV pandemic, and to define high risk populations, rates of maternal-infant transmission, and factors associated with increased risk of maternal-infant transmission. These studies provided the foundation for the evaluation of interventions to try to prevent maternal-infant transmission. Initial hopes for effective simple methods were diminished when vaginal cleansing with a disinfectant was shown to be ineffective in a carefully conducted placebo-controlled trial in Malawi. After the results of the first clinical study (ACTG 076) of zidovudine (ZDV or AZT) in pregnant women were announced, we and others had a great deal of optimism for the potential to prevent HIV infections among offspring of HIV seropositive women throughout the world.

Johns Hopkins University faculty have collaborated with developing country universities and Ministries of Health, the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH) to determine whether promising, affordable interventions are actually effective in preventing infections in developing countries. It soon became apparent that the ACTG 076 regimen is not feasible in most developing countries due to the complex schedule requiring early screening of pregnant women, intensive monitoring through pregnancy, intravenous infusions during labor, and continuing treatment of infants for 6 weeks. In many developing countries the majority of women have fewer than three prenatal visits and the vast majority of deliveries take place outside of hospitals.

In June of 1994, experts from developing and developed countries throughout the world reviewed the results of the ACTG 076 trial in a meeting at the World health Organization in Geneva Switzerland and concluded that:

> "....the ZDV (zidovudine) regimen employed in the ACTG 076 study has a number of features (cost, logistical issues, among others) which limit its general applicability. Therefore, no global recommendations regarding the use of ZDV to prevent MTI (maternal to infant) transmission of HIV can be made."
>
> "To increase the applicability of antiretrovirals in the reduction of MTI transmission of HIV, it is essential to explore simpler and less costly drug regimens in the full spectrum of HIV-infected pregnant women. Such regimens, including interventions restricted to the intrapartum period, should be urgently studied in randomized controlled trials."

and

> "Placebo-controlled trials offer the best option for rapid and scientifically valid assessment of alternative antiretroviral drug regimens to prevent MTI transmission of HIV."

Since that meeting, the issue of placebo-controlled trials to evaluate interventions for prevention of maternal-infant HIV transmission has been a source of discussion at numerous other international meetings and fora. After careful consideration, relevant ethical review boards have approved trials designed by the NIH, CDC, the United Nations and university investigators. These developing and developed country ethical review committees have not simply rubber stamped the protocols; they have insisted on numerous modifications in the studies and consent forms in order to assure that all ethical standards were met for each trial and that the studies were appropriate for each country.

Public Citizen has proposed that new treatments should be compared with the ACTG 076 regimen or that all women should receive some zidovudine. One of the basic ethical principles of any study, regardless of locale, is that the planned intervention must be potentially applicable in the locale or country where it is tested. The ACTG 076 regimen is not applicable in most developing countries. The alternative of giving all women at least some zidovudine in a regimen that might be applicable in the host country would likely result in uninterpretable results. Studies comparing the use of zidovudine in two or more untested short course regimens would have a high probability of finding similar HIV transmission rates in the two study arms. These results would be uninterpretable because we would not know what the rates might have been if no treatment were given.

Investigators carefully considered and rejected the possible use of historical controls to evaluate new interventions. Historical controls cannot be used because many factors affect the rate of transmission and these factors vary by geographic area and time. Rates of 14% to 40% have been documented in more than 10 observational trials. Since maternal-infant transmission rates have changed over time in the same area, investigators could not assure that lower rates of transmission in new uncontrolled trials are due to drugs or other products administered to the women or infants.

Public Citizen incorrectly implied that those engaged in the trials in question have double ethical standards. All review groups adhere to the same ethical standards. Hence, the criteria for justifying a randomized trial is the same in Africa as in the United States. What is different is the standard of care available in those two settings, not the ethical standards.

Public Citizen has misinterpreted the international guidelines for conducting research studies. The guidelines call for universal principles of ethical procedures, not universal standards of medical care. Imposing the US standard of medical care for all participants in international trials would prevent the United States and other developed nations from helping developing countries identify practical, feasible and affordable means for preventing and treating many diseases. Such a standard

would have prevented the development of two recently identified interventions that have dramatically improved the health of children throughout the world.

When oral rehydration therapy (ORT) was developed in Bangladesh, the standard of care for dehydration in the United States was intravenous fluids. In Bangladesh, however, very few people could afford intravenous therapy and little could be done for the vast majority of children with acute or chronic diarrhea. ORT has proven to be so effective that the standard of care in the United States has changed to emphasize ORT.

The vitamin A story is similar. When it became apparent that clinical vitamin A deficiency was associated with an increased risk of death, it was imperative to determine if subclinical deficiency was also associated with increased risk of morbidity and mortality. Large population-based clinical trials that used placebo controls convincingly demonstrated that high dose vitamin A supplementation could reduce childhood mortality in developing countries by 20%-35%. The control arm in these trials was not a fully balanced age-appropriate diet because that did not reflect the reality of the situation in those countries. The convincing evidence from these placebo-controlled trials has led to vitamin A supplementation as an integral part of child survival strategies world-wide.

Many other diseases are important causes of severe morbidity in countries throughout the world and effective, practical interventions are needed in developing countries to control heart disease, cancer and other problems. Trials of preventive or therapeutic interventions are needed, but it would be highly inappropriate to insist upon providing coronary artery bypass surgery, valve replacements or bone marrow transplants to developing country participants in clinical trials.

If the simpler, shorter course regimens of zidovudine or other simple interventions are shown to be effective for preventing maternal-infant HIV transmission, then it might be possible for developing countries to implement low technology interventions that would help control the HIV pandemic. The issues involved in designing and carrying out these studies are complex. Attempts to simplify the issues have contributed to confusion in the minds of some professionals and the general public. Your leadership in reassuring the Congress and the public that appropriate procedures have been followed and that the ongoing and planned studies are in the best interests of everyone involved, particularly the people of poor developing countries, would be most appreciated.

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James M. Tielsch, PhD
Professor,
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Health

Kenrad Nelson, MD
Director, Infectious Disease Program

NAH/bk

cc: Members of the House Subcommittee on Human Resources, Congresswoman Constance A. Morella, Congressman Elijah E. Cummings

UGANDA-CWRU RESEARCH COLLABORATION
Makerere University, Kampala
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Dr. Harold E. Varmus
Director, National Institutes of Health
Building 1, Rm 126
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Bethesda, MD 20892-0148

6 May, 1997

Dear Dr. Varmus:

It has recently come to our attention that the Government Reform and Oversight Subcommittee will convene a meeting on May 8, 1997, to hear testimony about the Alaska needle exchange program. Although not the stated purpose of the hearing, we are aware that testimony on the AZT studies in pregnant women in developing countries may be heard. Because researchers at Case Western Reserve University have been involved in the planning and implementation of such studies in Uganda, we would like to provide information about our current activities that relate to the comments made by the group Public Citizen.

Faculty members at Case Western Reserve University have been studying the impact of HIV infection on the men, women and children of Uganda since 1987. During this decade, we have fostered a relationship with members of the Ugandan Ministry of Health and Makerere University School of Medicine that is built upon mutual trust and scientific integrity. Research projects have been developed both to advance our fund of scientific knowledge about a devastating epidemic and to promote public health in the United States and Uganda. It was in the spirit of this mutual benefit that the studies for the prevention of maternal-infant transmission of HIV were first designed.

These studies, as all studies from Case Western Reserve University, have been independently reviewed and approved by ethical review committees both at Case Western Reserve University and in Uganda. In Cleveland, we have an institutional review board that meets all requirements of the Office for the Protection from Research Risks and is representative of the citizenry of the Cleveland. In Uganda, the AIDS Scientific Subcommittee and the Uganda National Council for Science and Technology comply with ethical standards required by the National Institutes of Health. The AIDS Scientific Subcommittee reviews all new proposals in the context of the Uganda situation and in the light of universal bioethical principles; the Uganda National Council for Science and Technology gives final approval. In the end, however, only the Ugandans can appraise the ethical nature of a proposed study in the context of their public health needs. It is not appropriate for Americans, whether they are scientists, or members of a government agency or advocacy group, to impose cultural mores or standards of care developed in the United States upon the resource-poor Ugandan health care system. Our Ugandan colleagues are ultimately the best qualified to weigh the ethical considerations involved in a study in their country, for it is they who are faced most directly by the opposing tensions of increasing medical knowledge while providing cost-effective sustainable health care. It is also their responsibility to protect their fellow citizens from exploitation, and foreign collaborators need to be sensitive to this issue.

We recognize that HIV/AIDS has challenged, and will continue to challenge, our capacities on every front, from the basic science to health care delivery. As we have made progress with our scientific agenda, we have not lost sight of evolving bioethical issues. Since at least 1994, in anticipation of vaccine trials and other intervention studies, faculty at Makerere University and Case Western Reserve University have worked together to revise ethical guidelines for the review of scientific research proposals in Uganda with support from the AIDS International Training and Research Program of the Fogarty International Center. In 1994, a 5-day symposium on bioethical principles governing clinical AIDS research was held with the Ministry of Health, the Uganda National Council on Science and Technology and the Ugandan AIDS Commission. The symposium included Ugandan participants from various agencies and commissions of the government as well as representatives from professional organizations. This symposium led to the definition of key issues for discussion and has been summarized in a recent publication (see attached). In July 1996, a second meeting of a core working-group was held to continue to refine the ideas first developed in 1994. This work will culminate in July 1997 when a national conference will be held in Kampala, Uganda, to review and approve a set of ethical guidelines for the HIV/AIDS era drafted by Drs. David Okello and Medi Kawuma of Makerere University School of Medicine and Sana Loue, J.D., Ph.D., of Case Western Reserve University.

The members of the Uganda-Case Western Reserve University Research Collaboration are committed to performing ethical, scientifically sound research that is beneficial to people in Uganda and the United States. In some circumstances, placebo-controlled trials may be necessary to answer important research questions. These placebo trials may be required when interventions that are proven effective in the United States cannot be readily transferred to the developing country setting because of biologic variability in disease, cost or limitations in the public health infrastructure. Properly designed studies, conducted by experienced researchers, can minimize the risk to all subjects involved in such studies.

The HIV epidemic affects all walks of life in Uganda -- men and women, the old and young, the poor and wealthy. It is fair to say that no one in Uganda has escaped the ravages of the epidemic. Many of those infected have lost hope and given up. Yet the presence of researchers, both Ugandan and foreign, sends an unspoken message that we have not conceded defeat but that there is still hope.

We would be pleased to provide further information regarding our activities if you are interested. You may contact Dr. Christopher Whalen at 216-368-3713 (or through a beeper: 216-464-8410, beeper 31868).

Sincerely,

Christopher Whalen

Christopher Whalen, M.D.
Assistant Professor of Epidemiology and Medicine

Jerrold Ellner

Jerrold Ellner, M.D.
Chairman, Department of Medicine
Professor of Medicine and Pathology

Fredrick C. Robbins, M.D.
University Professor Emeritus

cc on behalf of Dr. Thomas M. Daniel

Thomas M. Daniel, M.D.
Emeritus Professor of Medicine and International Health
Emeritus Director for Center of International Health
(Dr. Daniel contributed to the letter but was unavailable for signing)

Karen Olness, M.D.
Professor of Pediatrics

David Hopt, M.S.
Co-Director, Tuberculosis Research Unit

Robert Wallis, M.D.
Associate Professor of Medicine

Research Bioethics in the Ugandan Context: A Program Summary

Sana Loue, David Okello, Medi Kawuma

Researchers, scientists, and physicians in Uganda have become increasingly aware of the need to develop a systematic approach to reviewing biomedical research conducted in their country. Much of this awareness and their concern stems from Uganda's high seroprevalence of human immunodeficiency virus (HIV)[1] and the consequent large influx of research monies and HIV researchers from developed countries, including the United States and Great Britain.

We report on the proceedings of a five-day symposium on bioethical principles governing clinical trials, which convened in Jinja, Uganda in September 1994. The thirteen male and female workshop participants included representatives from the Uganda Ministry of Health, Makerere University, the Uganda AIDS Commission, Uganda's National Council of Science and Technology, and the National Chemotherapeutic Laboratory. These representatives included ethicists, physicians, researchers, and pharmacists, all of whom have conducted research themselves. Initial workshop sessions focused on the history of human experimentation and the development of protections for human participants in medical research, both in the United States and internationally. The workshop was intended as a first step toward examining Uganda's present system of bioethical review; the applicability of the principles of autonomy, beneficence, nonmaleficence, and justice to biomedical research in Uganda; and strategies for further development of a Ugandan code of research bioethics. Participants concluded that although these principles are relevant to research in Uganda, their adoption and implementation must reflect the circumstances and cultural context that are unique to Uganda.

Journal of Law, Medicine & Ethics, 24 (1996): 47–53.

Uganda's system of bioethical review

Uganda's current system of bioethical review developed, in part, in response to the increasing HIV research being conducted in that country. Current procedures require that research proposals be submitted for review to one of several committees, depending on the substantive nature of the research and on the site at which it is to be conducted. Hospital-based research, for example, must be approved by the hospital ethical committee of the sponsoring hospital, if such a committee exists. Research conducted through medical schools must be approved by the medical school faculty and postgraduate research committee of that school. These committees meet on an as-needed basis.

In addition, all research related to HIV must be approved by the AIDS Research Committee of the Uganda AIDS Commission and the National Council of Science and Technology (NCST). All biomedical research proposals must be approved by the Standing Committee of the NCST. This includes all HIV-related proposals, which must have received the approval of the AIDS Commission prior to submission to the NCST.

Proposals for research in Uganda which have been generated in the United States must also be reviewed by the appropriate institutional review board of the American institution that will be conducting the research. The Ugandan review process requires that proposals originating in the United States for drug trials to be conducted in Uganda must be reviewed and approved by the U.S. Food and Drug Administration.

Critics of these procedures have emphasized several areas requiring attention. First, membership on ethical review committees tends primarily to include physicians rather than individuals with expertise in diverse disciplines. As a result, the review committees often lack the ability to evaluate research proposals in the behavioral sciences. Sec-

ond, membership tends to be predominantly male, limiting the potential perspectives that are offered. Third, committees rarely include representatives from the research participant community, such as HIV-infected individuals, thereby depriving the committee of the perspective of the individuals most likely to be affected by the research efforts. Representation on the various committees is also often not reflective of the ethnic diversity in Uganda. Fourth, the committees are not always able to function as independently as they might wish, because of their ties with medical schools and government. Fifth, the review of proposals may require lengthy periods of time due to the lack of a quorum at meetings and to the absence of a financial and administrative infrastructure to support the functions of the review committees. Sixth, despite the committees' charge to review the ethical issues raised by the proposals submitted, the review often focuses on the scientific merit of the proposal and fails to examine the ethical aspects of the proposed research. Finally, the committees in Uganda have neither the legal authority nor a mechanism to ensure investigator compliance with the terms of an approved protocol.

The Ugandan cultural context of research bioethics

Social and economic inequality

Many participants in research studies are drawn from government-supported hospitals and clinics. Only physician visits and the cost of a room are provided without charge at these facilities. The overwhelming majority of patients attending government-sponsored health care facilities are poor and they cannot afford the fees for services such as x-rays, medications, and laboratory tests. Many of the patients are also illiterate. The population of these hospitals reflects the status of the majority of Ugandans; families often require two or three income-producing activities to survive economically.[2] Women, in particular, may be burdened by a lack of economic resources due to laws prohibiting their inheritance of spouses' or nonmarital partners' land and to family separation resulting from spousal illness or partners' maintenance of multiple households. A large percentage of patients may also be infected with HIV.[3] These conditions may lead a patient to feel that he/she really has no "choice" about participating in a study, which may well represent the only realistic mechanism for obtaining the requisite medical care or medications. Researchers and physicians, most of whom are significantly more affluent than their patients, may not fully comprehend either the circumstances faced by their patients or the subtle pressures that their patients may feel to participate.

History of colonialism

British economic, educational, and social policies from the late 1800s through the early 1960s resulted in the accentuation of ethnic and linguistic divisions in a country that is characterized by a multitude of nationalities and religions, and over forty languages.[4] Development occurred primarily in the south, and in the area of Buganda in particular. Buganda profited from the proceeds of cash crops. The first schools, begun by missionaries, were established in Buganda. The first class of Makerere College, established in 1922, consisted entirely of Baganda students, with many classes taught in the local language of Luganda. Non-Baganda students were not admitted until 1932. Thus the Baganda came to dominate the country as the result of both the economic and educational policies.[4] These inequities later reflected in Uganda's 1962 declaration of independence.[4]

The ethnic divisiveness, fueled by British policies favoring the Baganda, continues to be felt, despite Uganda's independence in 1962. Uganda's most educated and prosperous citizens are Baganda. Reviewers and researchers may not fully comprehend the circumstances faced by patients and potential research participants whose families and communities have historically been less favored. This may be particularly problematic in situations where a research review committee is composed primarily of members of one ethnic background, while the majority of research participants are of another ethnic group.

The legacy of tyranny

Since its independence, Uganda has been plagued by multiple forms of disaster, including famine, tyranny, widespread violations of human rights, epidemics, economic collapse, tribalism, civil war, and the collapse of the central government.[5] Milton Obote was elected Uganda's first prime minister in 1962. His regime was characterized by the increasing use of force to maintain stability. The commander of Obote's army, Idi Amin, staged a coup in 1971 during Obote's absence from the country. Amin's takeover was initially welcomed, based on his promises of a return to civilian rule.

Amin's actions were notably discordant with his words. Amin appointed himself president for life and began purging various factions within the military. In 1972, he forced Asian businesses to close and expelled all Asians from the country. The resulting economic disaster was followed by years of terror, during which Amin is estimated to have killed at least 300,000 Ugandans. His primary targets included the northern tribes, rival politicians, and the educated, including health care workers.

Obote, who had been in exile in Tanzania, returned to power (through a general election) in December 1980, following Amin's forced exile in 1979. Obote continued Amin's reign of terror with a pattern of detention, torture, and murder. The National Resistance Movement, led by

Yoweri Museveni, led an uprising against the government in 1982, plunging the country into civil war. Tito Okello successfully led a coup against Obote in August 1985. In January 1986, Museveni was sworn in as president, ending a fifteen-year period of war and terror.[9]

Until the Amin years, Uganda had had one of the best health care systems in Africa.[9] Government health facilities were well staffed, and drugs were available without charge. Between 1968 and 1974, however, the number of physicians and pharmacists decreased dramatically due to forced expulsion and emigration, resulting in a severe lack of drugs and trained medical personnel.[10] Uganda is now in the process of reestablishing an organized health care system, including various training programs for physicians, nurses, and health researchers.

Despite the generally high value placed on scientific research by members of the professions, popular reaction may be mixed. For example, some Ugandans believe that foreigners brought HIV to their country and that the foreigners are now exaggerating the impact of HIV as the result of a preoccupation with academic pursuits and a desire to devalue Africans.[11] The issue of HIV's East African origin has also created bad feelings among some Ugandans. The impact, if any, of these sentiments on the conduct of HIV research seems not to have been systematically examined.

The four principles and Ugandan culture

The Nuremberg Code of 1947 requires that biomedical research be conducted in a manner consistent with four ethical principles: autonomy, beneficence, nonmaleficence, and justice.[12] These four precepts have been reaffirmed in subsequent codes as an accepted basis for biomedical research.[13] Vigorous debate has recently arisen, however, about the appropriateness of applying this Western standard to biomedical research in developing countries and about the form that such application should take.[14] The proceedings at Jinja reflected similar concerns about the applicability of these concepts to Ugandan culture and, if applicable, about the manner in which they could be implemented.

The initial discussion focused on whether these four principles should be accepted as the basis for ethical review of biomedical research in Uganda; and, if so, how rigidly those principles should be applied. Participants unanimously accepted these principles as controlling, but favored a "context-sensitive application"[15] of the principles.

This modified casuistic approach is both pragmatic and sound. First, the concepts enunciated by the Nuremberg Code and the Helsinki Declarations are neither absolute nor clear.[16] In particular, the codes provide no guidance on how to resolve conflicts resulting from an attempt to maximize more than one principle simultaneously.[17] This difficulty may be particularly acute in Uganda due to its religious and ethnic heterogeneity. Second, a casuistic or case-based approach permits continuous reinterpretation and revision as new cases and circumstances arise.[18] Uganda's development of a process and method for reevaluation is critical in view of the major social, political, and economic changes now occurring. In sum, reliance on this modified casuistic approach will not only assure research participants of a required minimum level of protection, but will also permit a fuller consideration of diverse points of view and the idiosyncrasies of each case.

Autonomy

The Nuremberg Code and its progeny require that participants in biomedical research (1) provide consent to participate voluntarily, free from fraud or duress; (2) have the legal capacity to give consent; (3) be informed about the nature, duration, and purpose of the experiment, including the risks and benefits which may result; and (4) understand the information communicated to them.[19]

This concept of autonomy reflects the basic premise of individual sovereignty. Many cultures, however, subordinate the wishes of the individual to those of the immediate or extended family.[20] For instance, a sick person's family may decide whether the ill member should seek health care and from whom that treatment should be sought.[21] Similarly, in Uganda, the ability of an individual to participate in biomedical research may depend on the acquiescence or consent of another family member.

A difficulty in the interpretation and application of this principle is that somewhat conflicting legal and traditional practices govern consent. As an example, Ugandan civil law states that an eighteen-year-old male living at home has the legal right to make his own decisions. Customary law, however, dictates that the son obtain his father's consent prior to entering any obligation. Women are often economically dependent on their partners[22] and, in the experience of many working group members, often refuse to make a decision regarding their own participation or their child's participation absent the consent of their partner.

The working group resolved this apparent conflict between Ugandan custom and the Western concept of autonomy by recommending a mandatory waiting period of forty-eight hours between the time participation in a study is solicited and the informed consent form is signed. This would give the prospective participant an opportunity to review the information provided and to confer with others, should the prospective participant want to do so. The working group reached general consensus to the effect that a research participant must give his/her own consent to participate; another individual could not consent for an unwilling individual. A family member could, however, seek answers to questions—regarding a study's methodol-

formly demanded by Western funding sources.[18] Finally, past experience has demonstrated that, in the context of research, the four principles work more or less to effectuate their goal: the protection of research participants. The working group's suggested repackaging of these principles to incorporate local customs and traditions offers several potential benefits, including the alleviation of fears associated with the adoption of a foreign-mandated code and the development of greater understanding and respect between Ugandan and Western researchers and their research participants.

A significant amount of work remains. Additional perspectives must be included in the development of a bioethical review process, including those of the judiciary, the religious communities, and the legal community. Concepts must be phrased and reexamined in a context appropriate to Uganda and its citizens' sensibilities. For instance, "free choice" may be more easily discussed and implemented as "self-determination," which appears less selfish and individualistic, and more easily incorporates familial and societal considerations.[19] The balance of power in consent negotiations must be more fully explored, including perceptions of consent and decision making in particularly vulnerable or insular populations and the role of reciprocity in these negotiations.[20] Guidelines must be developed, disseminated for comment, and revised prior to formal publication and implementation.

The process of developing ethical guidelines for medical research in Uganda will continue for some time. The strategies now being used to develop them may provide a blueprint for other countries engaged in a similar examination.

Acknowledgments

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We gratefully acknowledge the critical review by Drs. Jerrold Ellner, Karen Olness, Sandra D. Lane, and Christopher Whalen of earlier drafts of this manuscript.

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HARVARD SCHOOL OF PUBLIC HEALTH

Department of Nutrition

May 7, 1997

Harold Varmus, MD
Director,
National Institutes of Health
Office of the Director. Building 1, Room 126
Bethesda, MD 20852

Subject: Public Citizen report of April 1997 on trials to evaluate the efficacy of interventions to reduce mother-to-child transmission of HIV infection

Dear Dr. Varmus:

We are writing to express our concern about the recent Public Citizen report that labeled as unethical most of the ongoing HIV prevention trials in various countries of the developing world, including a trial that we are implementing in Tanzania.

We are carrying out a trial to examine whether vitamin supplements reduce the risk of mother-to-child transmission of HIV-infection. In observational epidemiologic studies, vitamin A-deficient women were at an increased risk of transmitting HIV infection to their babies compared with women who had sufficient levels of vitamin A. In a number of studies, poor status of vitamin A and other vitamins were associated with lowered immune function, possibly leading to a higher risk of transmission of the virus.

Our study was approved by 3 different ethical committees: the Ethical Clearance Committee of Muhimbili Medical Center, Dar es Salaam, Tanzania; the Ethical Committee of the Tanzanian Ministry of Health; and the Institutional Review Board of Harvard School of Public Health. We regret the fact that the Public Citizen group feels that it is in a better position to decide what is ethical for HIV-infected women, when the Tanzanian ethical committees have deliberated at length and decided that the conduct of the trial was in the best interest of their people.

We do not question the right of HIV-infected pregnant mothers everywhere to receive the best preventive intervention. The immediate concern, however, is that the ACTG 076 regimen is unaffordable to most of African countries, including Tanzania where the annual per capita health expenditure is less than $3.50. Therefore, low-cost interventions are urgently needed. Vitamin supplements are one of the few potential interventions which are inexpensive enough to be made available to people in developing countries. The efficacy of short-course, and relatively more affordable, antiretroviral therapies should also be evaluated in these settings.

665 Huntington Avenue Boston, Massachusetts 02115 Tel: (617) 432-1333 Fax: (617) 432-2435

Assuming that ACTG 076 regimen were affordable, its efficacy in reducing the risk of mother-to-child transmission of HIV infection has not been examined in a breastfeeding population. Providing this regimen in countries where breast feeding is common for upto 2 years of age, would require the introduction of artificial feeding of the infant from birth. This change in breastfeeding policy is unaffordable, in addition to being associated with a higher risk of morbidity and mortality.

Our institutions have been involved in collaborative research and training in the public health field for the last 20 years, more recently focusing on issues related to HIV infection. The National Institutes of Health have been instrumental in supporting our efforts, and those of colleagues at other universities in the US and in developing countries where HIV infection is a serious problem and the interventions to limit its spread are limited. We count on your leadership in allaying the public anxiety that may have been created as a result of the recent Public Citizen report.

Sincerely,

Wafaie W. Fawzi, MD, DrPH
Assistant Professor, Harvard School of Public Health

Gernard I. Msamanga, MD, ScD
Senior Lecturer and Chairman, Department of Community Health
Muhimbili Medical Center, Dar es Salaam, Tanzania

David J. Hunter, MD, ScD
Associate Professor, Harvard School of Public Health

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Division of Disease Control

May 7, 1997

Dr. Harold Varmus
Director
NIH
Office of the Director
Building 1, Room 126
Bethesda, MD 20852

Dear Dr. Varmus:

As I believe you are aware, I am the Principal Investigator of an HIV intervention trial that is to be conducted in Addis Ababa, Ethiopia. In the recent news release from the Subcommittee on Human Resources, there is a sentence that states "Critics claim an AIDS drug trial being conducted in Africa lacks informed consent and increase (sic) the risk of infection of some infants." Ms. Pettengill in our Public Affairs Office was told by one of Congressman Shays staffers that this statement referred to our study being conducted in Ethiopia. Should this issue be brought up in tomorrow's hearing, I wanted to provide you with specific information to refute this statement.

First, the trial has not yet begun. With regards to informed consent, it is important to point out that as a former vice-Chair of the Johns Hopkins University School of Hygiene and Public Health's IRB, I believe very strongly in the principles of informed consent and have worked diligently to optimize the process in our study. Therefore, we have established the following for our study in Ethiopia:

1) We have 2 consent forms, one for HIV screening and one for enrollment into the trial. These forms have been reviewed and revised in country, have been translated into Amharic (the local language) and back-translated into English several times with appropriate revisions being made at each step. All women attending the prenatal clinics will be provided with group education regarding HIV. They will then meet individually with a counselor who will provide additional information regarding HIV and the clinical

trial. Any woman agreeing to sign the consent form will be asked a series of questions to be certain that she has understood the content of the consent form. If she cannot answer the questions correctly, the counselor will review the consent form with her again.

2) The counselors who will be involved with our project have had intensive training that involved role playing, and video taping, as well as educational sessions regarding HIV. The training supervisors will do regular monitoring of the counseling to ensure that the counselors are doing a good job.

3) We have asked Dr. Michael Sweat, a medical anthropologist to work with us on this project and to specifically evaluate the effectiveness of our HIV education and counseling process. He and his Ethiopian colleague will provide feedback on our existing consent procedures, including the cultural appropriateness of the process.

Finally, while our study does include a placebo arm, there is nothing in it that could "increase the risk of infection of some infants". Thus, the entire statement in the news release referring to our study is factually incorrect.

Thank you for your attention to this matter and please let me know if you have additional questions.

Sincerely,

Andrea J. Ruff, M.D.
Associate Professor

Attachment: Subcommittee on Human Resources News Release (May 2, 1997)

UGANDA CANCER INSTITUTE
P.O.BOX 3935
KAMPALA
TEL:011-25-41-540-410
FAX:011-256-41-532-282 or 011-256-41-500-188

Date:May 8, 1997

Dr.Harold Varmus
Director, National Institutes of Health
Bldg 1, Rm 126
8000 Rockville Pike
Bethesda, Maryland 20892

Dear Dr.Varmus,

Subject: Public Citizen News Release.

I have read with dismay and disbelief the above mentioned document regarding Clinical Trials in developing countries with special emphasis on those taking place in Uganda.

It raises various issues which I would like to address:

Policy: Because of the different economical capabilities, policies regarding health management differ between industrialized and developing countries. Whereas it is policy that all pregnant women in the US and other developed countries get AZT, this is not possible in many developing countries today. To expect any of these countries to afford the cost of AZT as given in ACTG 076 is not realistic. It follows therefore that developing countries need to conduct research that will generate results which will have practical applications and relevance to the practice of medicine and affordable cost of medicare in those countries. It is the policy of our government to collaborate with international institutions and agencies in health research.This collaboration should not be viewed as a sign of weakness. We are not coerced into carrying out any research.

Inadequacy of the current review system: It has been suggested that some IRBs are composed of researchers who because of different social classes and for selfish reasons cannot safeguard the interests of their citizens. This level of patronizing is in my opinion uncalled for. For instance in Uganda our IRB for AIDS research of which I am the chair, if conflict of interest arises the researcher concerned is recused. It is a wrong assumption that we do not have the vision to deal with such issues.

Tuskegee Part two: It is very unfortunate that this comparison has been made at all. It dramatizes and ignores the facts at hand. Ugandan researchers are PIs on these protocols and the local IRB approved them after scrutiny.

International Ethical guidelines in Biomedical Research:

The last paragraph on page 7 of the International Ethical Guidelines for Biomedical Research Involving Human Subjects reads as follows" The mere formulation of ethical guidelines for biomedical research involving human subjects will hardly resolve all the moral doubts that can arise in association with such research, but the guidelines can at least draw the attention of investigators, sponsors and ethical review committees to the need to consider carefully the ethical implications of research protocols and the conduct of the research, and thus conduce to high scientific and ethical standards of research."

The studies under consideration are designed to respond to the needs of the developing world namely slowing down the transmission of HIV from mother to child thus reducing on the burden of disease in these countries. They are in conformity with Guideline #8 which states as follows" Before undertaking research involving subjects in underdeveloped communities, the investigators must ensure that ..... the research is responsive to the health needs and the priorities of the community in which it is to be carried out; every effort will be made to secure the ethical imperative that the consent of individual subjects be informed; and the proposals for the research have been reviewed and approved by an ethical review committee that has among its members or consultants persons who are thoroughly familiar with the customs and traditions of the community."

Insensitivity of news release: This release ignores the magnitude of the HIV epidemic especially in Africa. It forgets how poorly the health sector is financed in developing countries and the countries' desire to come up with affordable effective treatment regimens.

Ethical Imperiliasm: These are Ugandan studies conducted by Ugandan investigators on Ugandans. Due to lack of resources we have been sponsored by organizations like yours. We are grateful that you have been able to do so.

There is a mix up of issues here which needs to be clarified. It is not NIH conducting the studies in Uganda but Ugandans conducting their study on their people for the good of their people. If this is not acceptable and the only way to do it is that which has been suggested in the news release, then this is tantamount to ethical imperiliasm.

Design of the study: AZT given in ACTG 076 study is considered the "gold standard". For a moment let us assume that it was our "control arm" of the study. If the results of the study showed that the transmission rates in other arms were less than 66%, what would be our inference? Obviously we would say that those treatments are inferior to AZT and therefore not recommended. Just imagine what would happen if they reduced transmission by half using the placebo as the reference point. The reaction and recommendations would be different!
I would like to quote Guideline # 10 which states as follows"Individuals or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed." We are of the view that our studies fulfill this requirement.

In summary therefore, these studies are a priority of Uganda's efforts in controlling the spread of the epidemic. Furthermore they conform to high scientific and ethical standards interpreted in the light of the epidemic and financial resources available to cater for the ever growing need in our country. In approving them we have been guided by our needs, the international accepted ethical principles and at the same time rejecting "ethical imperialism".

Sincerely yours,

Edward K.Mbidde, MBCHB
Chair,
AIDS Research Committee

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8 May 1997

Dr Harold Varmas
Director
National Institutes of Health
Building 1, Room 126
9000 Rockville Pike
Bethesda, MD 20892
USA

Dear Dr Varmus

It is interesting to have heard and read about the debate that is currently ongoing in the United States about the ethics of conducting AZT interventive studies in developing countries. As a scientist in South Africa involved with research that is supported by international institutions I thought that it is necessary for me to express some opinion on the matter.

In South Africa the HIV epidemic is having a major public health impact. The National Department of Health has just last week released the results of the 7th national survey of women attending antenatal clinics. Nationally approximately 14% of women were found to be HIV positive and in some areas, which are predominantly the most disadvantaged in the country, the rate in excess of 25%. Extrapolating from these figures, estimates are that that approximately 70000 HIV infected infants will be born this year.

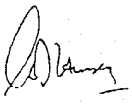
The result of the 076 trial was extremely heartening. AZT successfully reduced the rate of vertical transmission. The major problem for virtually all countries in Africa is that the 076 trial regimen and cost of AZT precludes its routine use. Even in South Africa, given its material wealth, it would probably be impractical. If AZT (or any other anti-retroviral agent) is to be used as a strategy to reduce perinatal transmission then a more cost effective regimen must be developed. The only way to prove the efficacy of such an intervention would be in a placebo controlled clinical trial.

Public Citizen has accused American researchers of violating international rules of ethical practice by supporting placebo control clinical trials in developing counties. By implication they are accusing the researchers in these countries of doing likewise. Many of us who (as health activists) have been involved in the struggle for democracy in health under the old apartheid regime in South Africa will be offended by such accusations. In South Africa two clinical trials are currently taking place and is being conducted by scientist from within the country. One is evaluating anti-retrovial therapy and the other vitamin A therapy. Many of us do not see these trial as violating ethical norms. My colleagues involved in the trial are responsible scientist and the project has undergone a stringent ethical review process. Many of persons involved in these studies are AIDS activists and are not involved for personal gain or glorification. In addition the Department of Health under the Mandela government has given the studies its full support

The efforts of organisations who speak up for and who are attempting to protect the interest of the oppressed and exploited in developing countries are to be commended. In the context of the current debate it would have been more constructive to have obtained the viewpoint of those who are being spoken for and those (the researchers in developing countries) who are being accused of violations of ethical practice. There will always be controversies relating to the conduct of placebo control clinical trials in developing countries. Given the available scientific data and taking into account the problems of delivering health care in developing countries, such studies can help define the most appropriate cost-effective interventive strategy.

The debate on anti-retoviral therapy clinical trials in pregnancy has been raised. Hopefully the matter will be resolved in a constructive manner. This is not the only problem. There are numerous other moral and ethical dilemmas that confront all of us involved in AIDS work. In the context of AIDS treatment should we not be harnessing our energies to get the pharmaceutical companies to reduce the costs of anti-retrovirals and thus make these drugs accessible to all?

Yours sincerely



Associate Professor Greg Hussey
Senior Specialist and Head of Paediatric Infectious Diseases Service.

Mr. TOWNS. Thank you very much.

Mr. SHAYS. Thank you. Mr. Kucinich.

Mr. KUCINICH. I just have a quick question of Dr. Varmus. If NIH believes that only placebo controlled studies can provide answers to the questions most relevant in developing countries, why then is the NIH funding one Harvard study in Thailand in which no women will receive a placebo and all with receive anti-viral drugs?

Dr. VARMUS. Well, we don't believe that that is the only way to achieve results. Thailand, of course, is a somewhat different situation than some of the African countries we're discussing today, because of the more—the stronger economy and the ability of the country to provide drugs that are more expensive and would be unaffordable in Africa.

Mr. KUCINICH. And if it's true that using placebo controls reduces the number of subjects needed to demonstrate statistical significance, why does NIH funded non-placebo controlled study in Thailand anticipate in enrolling fewer subjects than the U.N. AIDS program study in Tanzania, Uganda and South Africa? For example, you have, I think, 1,554 subjects in Thailand versus 1,900 in a combined U.N. AIDS study.

Dr. VARMUS. 1,500 subjects being enrolled in Thailand. I'm not quite sure what the question is, Mr. Kucinich.

Mr. KUCINICH. I'm asking why, if you are using placebo controls—if you're saying that reduces the number of subjects that you need to have statistical significance—do you agree that you do that?

Dr. VARMUS. Yes.

Mr. KUCINICH. OK. Then why do you—why does this funded non-placebo controlled study in Thailand anticipate enrolling fewer subjects than the study that's going on with the U.N. AIDS program in Tanzania, Uganda, and South Africa. I'm trying to compare your policies with the other.

Dr. VARMUS. I would have to look at the details of the protocols more closely to give you a direct answer to that question. I'd be happy to do that for the record.

[The information referred to follows:]

Insert for the Record of the May 8, 1997, Hearing before the House Government Reform and Oversight Subcommittee on Human Resources, page 82, lines 1843-1847.

Response to Question Raised by Representative Kucinich to Dr. Harold Varmus, Director, National Institutes of Health:

Before any clinical trial is started, it is essential to estimate as precisely as possible the number of study participants that will be required to answer the question of whether or not the treatment being studied is effective. There are a number of factors that go into a statistically-based estimation of how many study participants will be required. These factors include:

1) how large is the impact of the treatment expected to be? That is, is the treatment expected to be 100 percent effective or 50 percent effective or less effective?

2) how certain do the investigators wish to be that their finding at the end of the study is in fact real and did not occur by chance alone?

3) how common is the occurrence of disease that the investigators are seeking to reduce? For example, if a certain disease outcome happens in 40 percent of people exposed and you wish to reduce this occurrence such that it occurs only to 10 percent of the people exposed, you need a much smaller number of study participants than if a certain disease outcome happened in 10 percent of people exposed and you are trying to reduce it to 2.5 percent of the people exposed with the treatment you are studying. In both of these cases, the reduction you are trying to see is a four-fold reduction, but many more participants will be needed in the latter versus the former case.

Other issues that come into play in determining the number of study participants include how many participants may be lost to follow-up before the end of the study.

The two studies referenced in this question are very different studies. One study (the UNAIDS study which is placebo-controlled) is looking to see whether or not two drugs used together (ZDV and 3TC) can reduce mother-to-infant transmission of HIV. This study is ongoing in several sites in Africa and is comparing three different regimens of the two-drug combination against placebo. In this study, the mothers will be breast-feeding their babies after delivery. In the other study (the NIH-supported Harvard study in Thailand), one drug (ZDV) is being studied in four different types of regimens. The mothers in this study will not breast-feed their babies after delivery.

In putting together their sample size calculations in planning how many women would be needed to participate in their studies, the investigators of the two different studies used the three factors listed above. In addition, they made some estimate of the number of women who might not complete their study. Because some of the factors that go into calculating the needed number of subjects are very different when comparing Thailand to multiple sites in Africa, the investigators reached different estimates concerning the number of study participants needed.

Mr. KUCINICH. OK. I'll pass for now.

Dr. SATCHER. I may have contributed to some of the confusion. There are two or three reasons why we feel the placebo control studies are important and I'll just briefly mention them. You know, I mentioned what the countries are wanting to learn from these studies. One issue is safety. They want to be certain that AZT is safe as it relates to the mother and a developing fetus. And it's a question that can only be answered by using, from our perspective, placebo controlled studies. We can't answer it satisfactorily comparing short-term dose with a long-term dose of AZT.

I gave one example of that. There are also complicated statistical reasons why we couldn't answer that question using short-term AZT comparing it with long-term AZT. And so I think there are questions that the host countries have asked that we can only answer, certainly in Africa, by using the placebo controls.

Mr. KUCINICH. Well, one quick followup based on this colloquy with Dr. Varmus. Did you say that using the placebo controls is not the only way to do a study?

Dr. VARMUS. You can get information. It may be less reliable. It may take more enrollees. Again, I don't know the details of the protocols you're alluding to. One obvious reason why the study populations might differ in size is because of the frequency of infection or the prevalence of infection in those populations.

Mr. KUCINICH. Do ethical considerations come up when you get into those matters?

Dr. VARMUS. They might depending, again, on the availability of support systems to provide the drugs that might be used.

Mr. KUCINICH. Would you advocate that the most ethical way always be used in designing your protocols?

Dr. VARMUS. Well, I think you have to be clear about what the most ethical way is.

Mr. KUCINICH. Yes, we do. That's what we're here.

Dr. VARMUS. Yes. I know. But it can be difficult. It may vary from country to country.

Mr. SHAYS. Gentlemen, we're going to probably need to ask questions for another 30 minutes. We have a vote now. I'd like to say to the second panel it's very unlikely that we would get to you before 1 o'clock. And so you may want to get something to eat. We're going to have a vote and we're going to come right back. We consider this an expert panel.

Not to be compared to many others we have had. You are an excellent panel and we really want to get some things on the record. So we're going to vote and come back. We may then end up with another vote 10 minutes later, and I apologize. But we'll make the best of it. So I would just say to the second panel, if you're back by 1 o'clock, we'll begin with the second panel at 1 o'clock. I don't think sooner. And so you don't need to be here sooner. I want to be clear. Second panel does not need to be here before 1 o'clock. We stand at recess.

[Recess.]

Mr. SHAYS. Dr. Raub, let me start with you and ask why has HHS not abided by the regulations by making appointments to the Ethics Advisory Board? And it goes back a long ways. I'm not

throwing stones here. But it goes back to 1979. I'd like the short reason.

Mr. RAUB. I'll do my best, sir.

Mr. SHAYS. OK.

Mr. RAUB. The Department believes that it is operating in conformance with both the law and the regulation with respect to the Ethics Advisory Board. The 1975 regulation did several interrelated things: It imposed strict limits on research with fetuses and with pregnant women; put an outright ban on in vitro fertilization research; and then defined a process for exceptions. And the Ethics Advisory Board, or boards, were the vehicle where exceptions could be considered to either the ban on in vitro fertilization research or the restrictions on research with fetuses and pregnant women.

Mr. SHAYS. I had interpreted the Ethics Advisory Board had broad discretion over ethics in medicine, not limited to just a certain area.

Mr. RAUB. The regulation is framed where the secretary has the discretion to have an ethics advisory board for specific tasks of that sort or for a broad set of issues.

Mr. SHAYS. So it's not one board that's supposed to make a ruling on lots of different issues?

Mr. RAUB. No, sir. The regulation allows for the possibility of several different boards.

Mr. SHAYS. Or just one.

Mr. RAUB. Or just one.

Mr. SHAYS. Yes. But why would it be in our best interest to establish commissions and not have a board that is fully funded and has a staff. For instance, you're getting an executive director, basically a replacement—you're acting as the executive director, correct, of the commission?

Mr. RAUB. Yes, sir.

Mr. SHAYS. And I don't understand why that would be a logical way to proceed. It seems too ad hoc to me.

Mr. RAUB. OK. Well, one of the options available to the administration was to invoke the secretary's authorities to create an ethics advisory board. And it could have addressed essentially the same agenda that the NBAC is. However, we view it as clearly more desirable for this to be a Presidential level commission, especially giving it the span of involvement of multiple agencies in the Government that are involved in research on human subjects.

Mr. SHAYS. How many people are employed on this board?

Mr. RAUB. There are 17 members of the board, 17 commissioners.

Mr. SHAYS. Yes.

Mr. RAUB. And the staff supporting it involves eight full-time staff and four who are part-time.

Mr. SHAYS. Now, your testimony, I thought, said it continues or authorized until, what, October?

Mr. RAUB. That is correct.

Mr. SHAYS. What's the logic of that?

Mr. RAUB. The Executive order signed by the President covered 2 years from the date of the President's signature. And the Executive order allows that it expires on that date unless extended by an Executive order.

Mr. SHAYS. Right. So what's going to happen?

Mr. RAUB. Well, the administration is now considering extending the NBAC charter via amendment to the Executive order because of the additional work load that has developed and because of the additional issues that have been identified.

Mr. SHAYS. Well, it seems to me like a no-brainer that we need this work done. I don't quite understand why this wouldn't be a permanent board. In other words, when I'm looking to see what we have, we have basically local institutional review boards. We have those. We have the institutes of health and their boards and we have the Ethics Advisory Board not constituted. I see a gigantic void here. And you don't see a big void?

Mr. RAUB. Sir, I believe you'll find many advocates within the Government as well as outside for the notion of a continuing body with functions similar to that of NBAC to address these issues just in the way you're suggesting. Many are looking to the experience with NBAC as getting additional evidence and information as to the desirability of such a board. And I believe that's one of the major issues under consideration right now.

Mr. SHAYS. Why would someone take a job that basically they're not guaranteed that they're going to have it go until October?

Mr. RAUB. I would share that concern, sir. And we're hopeful that by the time we are ready to make a selection we will have had some resolution as to the extension of the board.

Mr. SHAYS. OK. Dr. Satcher, what specific steps would your agency take to detect what is called the—I guess we call it the therapeutic illusion. Really, let me ask it in the way I think makes sense to me. Some testing is a healing agent, and you want to test whether it really succeeds in doing what it's projected to do. Others you might just do testing for safety. How do you notify someone in a clinical trial that really all they're doing—they may get sicker, we just want to know if it's safe? What are the requirements that you feel have to be made ethically?

Dr. SATCHER. Let me say that in most cases we're asking both the efficacy and the safety question. It's just, again——

Mr. SHAYS. But not always. And I want to be clear. The only reason I would participate in some kind of clinical test is the thought that I might get healed and I'm willing to take the chance. And you're going to warn me of all the potential downsides and I'm still going to do it. But I want to know if there is a requirement to tell someone that along with talking about, well, this may not be safe here, there's no promise that it's going to help you?

Dr. SATCHER. I think definitely we're required. And the informed consent form should make that very clear, that they are involved in a study that may not benefit them personally at all. And if an informed consent form does not make that clear, then I would say that it's inadequate.

Mr. SHAYS. Dr. Varmus.

Dr. VARMUS. Mr. Shays, I think you're referring mainly to phase 1 clinical trials for which NIH probably has more responsibility than the CDC.

Mr. SHAYS. Right.

Dr. VARMUS. Our consent forms do explicitly make clear that there is no intent to—no expectation of clinical benefit. This does not exclude the possibility of there being benefit, but the expecta-

tion is that they will be testing here for safety. That will allow some determination of what doses might be used, and then you can proceed into a phase 2 trial.

Mr. SHAYS. Are you suggesting, though, that there may still be the hope that the person has that this could result in some healing benefit?

Dr. VARMUS. There is in some cases that possibility, but we stress to the patients in these very limited studies that the intent of the phase 1 is to establish safety and that they are performing a service through their participation and research. This is why we take these consent forms so seriously, particularly in that phase of the experimentation.

Mr. SHAYS. Now, with the Office for Protection from Research Risk, that basically is an in-house. I'm trying to understand——

Dr. VARMUS. The OPRR——

Mr. SHAYS. I'm trying to deal with the issue of how you avoid a conflict of interest. You're an independent "watch dog." And yet, you're basically providing for research. You're involved in the whole ethics of whether it's allowed, but you're funding it.

Dr. VARMUS. Well, let me address that issue, Mr. Shays.

Mr. SHAYS. I'm sorry?

Dr. VARMUS. Let me address that issue.

Mr. SHAYS. OK.

Dr. VARMUS. The OPRR does provide oversight for activities that are carried out by the NIH institutes and also by the CDC and FDA and other organizations within the Department. It has administrative housing and some administrative oversight from Dr. Baldwin's office, the Office for Extramural Research. It's important to remember that the office does not have any vested interest in seeing the research go forward in the sense that my office would be funding the research. The research is being funded by the CDC or by institutes, each of which has its own authorization and its own appropriation. It is the institutes that are responsible for funding those studies. So there really isn't the conflict of interest that I think you're——

Mr. SHAYS. I'm missing something. Because it's the same organization. You're just saying a division within the organization.

Dr. VARMUS. Well, there is fiscal independence and a responsibility for funding a study that lies outside of the office of the director in which the administrative housing occurs.

Mr. SHAYS. And you're satisfied that that would meet an independent's test?

Dr. VARMUS. I think it does. As you heard from Dr. Raub, I was concerned about having the NBAC housed within the NIH because the NBAC is, of course, looking at much broader issues that establish the principles in which informed consent or protection of individuals of abuse of genetic information might be carried out. The OPRR is following regulations that were issued by the Department. And it's governing compliance with already established rules and regulations.

Mr. SHAYS. Doctor, do you believe that mentally ill individuals and those who are addicted should have a different protocol, should be covered explicitly by HHS regulations?

Dr. VARMUS. Yes, but special care needs to be taken in overseeing studies that involve patients that may be cognitively compromised. I discussed that in my testimony. This is a very difficult issue, which accounts for the large number of studies and work shops and consultations that the institutes involved in such studies are involved in.

Mr. SHAYS. With regard to Alzheimer's patients, do you have written guidelines for informed consent?

Dr. VARMUS. The National Institute on Aging, which has a major responsibility for such patients is working on such guidelines. They will be participating very actively in the upcoming work shop this fall in which we expect to confront the issue of consent in such patients as a special case study during the proceedings.

Mr. SHAYS. Why wouldn't have that already occurred?

Dr. VARMUS. Attention has been given to it. But, of course, there is always the need to proceed further and evaluate what has been done. We were not oblivious to the fact that patients with cognitive disorders of aging present special problems. But we do believe that as we gain increased experience, we should be profiting from that by further contemplating the issue.

Mr. SHAYS. This is an issue, Dr. Satcher that you have already addressed. But I want to just clarify it for when we write a report or recommend legislation. It deals with generally the issue that was being raised by my colleagues of trials done overseas. And I'm gathering that in Thailand the CDC is funding placebo control trials.

Dr. SATCHER. Right.

Mr. SHAYS. And the answer is yes to that. The NIH has another program where there's no placebos. And I think I heard your response, which I'm not critical of, because I'm just—I may be critical of it, but it seems like an interesting issue to deal with; you're saying that overseas some patients wouldn't have gotten AZT anyway.

Dr. SATCHER. That's exactly right.

Mr. SHAYS. Pardon me?

Dr. SATCHER. It's not the standard of care.

Mr. SHAYS. Right. But isn't there an incredible temptation that we have to be careful of, of suggesting that a lot of things, health care that people don't get overseas——

Dr. SATCHER. Yes. I think you're right.

Mr. SHAYS. And it almost becomes your proving ground—the rich United States with all our good laws and all the medicine that's available to American citizens. But overseas you can say, you wouldn't have had this anyway, so you're not losing anything. And I'm just curious how we sort that out. Because I think it's potentially a dangerous road to travel.

Dr. SATCHER. I think so. I think it's a complex issue. And I think it has to be looked at just as you have described it. Let me say that there is an international community involved here, and it's not just the United States. I think the U.N. AIDS program, which is very important in this, as well as the World Health Organization have both looked at the AZT regimen that we use in this country and that's used in some European countries.

I think the critical issue—and I think it's referred to in the international guidelines for research—has to do with the host country

and the extent to which the research is meeting the needs and interests of the host country and is going to result in benefit for the host country. I think these are really the key issues that we're struggling with when we try to resolve the question that you raise which is so important—To what extent will the host country benefit from this study? To what extent are they asking the questions that your study is seeking to answer?

Mr. SHAYS. Yes.

Dr. SATCHER. History is very important as you know. And we were just talking earlier when you were away that the hepatitis B vaccine studies that were done in China in the early 80's—very similar to what we're discussing now in Africa and Thailand—a major problem in China—hepatitis B. We had the immune globulin in this country. It was a little different situation in terms of what we were able to afford and what was being used. However, that study was very important and of great interest to the Chinese. Of course it resulted in showing the efficacy and safety of the hepatitis B vaccine.

It's benefited China significantly, but it has also benefited us. And as you know now, it's a major part of our vaccine regimen in this country. But it was done because of the interest of the Chinese primarily. The same thing is true here in terms of the short course of AZT therapy. Obviously, the interest of the people in the Ivory Coast and in Thailand is that we don't feel that we can use the 076 regimen. We would like to know if there's another way we can use AZT to intervene to prevent the spread of AIDS from mother to child. Is there a cheaper way? Is it safe? Is it efficacious?

Mr. SHAYS. I just want to highlight the issue, though, that it's almost this imperialism of the United States of having one standard overseas and another standard here because we say, well, it's a different culture, different society, different wealth, different standards. And then we can then end up doing things there that we would never conceive of doing here.

Dr. SATCHER. I don't think we should unless it's in the interest of that country and unless that country is making it very clear that it's in their interest and it responds to their questions. I understand your point. And I agree that there is a danger that we could, in fact, exploit other countries.

Mr. SHAYS. OK. I'm going to ask the other two to followup. At the same time I'm just going to ask this question: Do infrastructure problems of malnutrition and poor water supply ultimately distort the finding of a clinical study that may give us a result different overseas than in the United States? But I'd like the first question—I'd like all three of our other panelists to respond to the ethics of experiments overseas based on different laws overseas and based on lack of wealth that says that they would have been denied certain health care that they would get in this country. Dr. Raub.

Mr. RAUB. Well, first of all, Mr. Chairman, I agree with your principle that we must be sensitive from the beginning and all through that what we may pursue with the best of intentions and compassion might somehow slip into being exploitive or imperialistic. And so that must be a caution all the way through. From my point of view I believe there are four principles that affect these

studies. My colleagues have spoken to them in various ways. But just very quickly.

That the treatment that is involved, in the judgment of experts, have a reasonable chance of working; that the treatment be well matched to the health care system of that host country, that is something that could be adopted and become the standard of care if the results of the trial were sufficiently positive. Third, that the placebo control be used only when necessary, that is only when the historical information is so bad that it would be worthless and would not lead to either good science or an ethical study. Finally, that there be full participation of public health officials in that host country from the beginning, in terms as Dr. Satcher was indicating—the design of the studies and the implementation.

I believe that those four principles can be held through with systematic use of IRBs and wherever possible to avoid the conflicts of interest. Then I think we have an excellent chance of doing things that are good both for the host country and this Nation.

Mr. SHAYS. And I'm going to come back to the infrastructure issue and the malnutrition issue in a second. Dr. Varmus.

Dr. VARMUS. Mr. Chairman, I don't want to reiterate what has been said, but I also would point out that the issue of exploitation, which is that one that's currently being addressed, presents a number of problems. Perhaps the most egregious of these, in my view, would be to carry out in a developing country a trial which only produced results that would be of benefit elsewhere and not in that country. That's why the design of the studies we're talking about need to be one that could lead to an outcome that would be beneficial to the country in which the study is being carried out.

Mr. SHAYS. So that would be a primary determinate for all three of the panelists. Ms. Pendergast, do you want to comment on this issue?

Ms. PENDERGAST. No. I would just reiterate the comments of my colleagues. I think we all recognize that this is an incredibly complex ethical and scientific question that reasonable minds can and do debate. And I think that the debate is healthy. And I think it behooves us all to continue to critically explore these issues to make sure that we are on and stay on the proper path.

Mr. SHAYS. OK. It's my intention to end at 1 o'clock. Dr. Varmus, you have to be over there at 1 o'clock?

Dr. VARMUS. I believe so. Yes.

Mr. SHAYS. OK. We'll make sure you have a car ride over and get you over there unless you have 10 people with you.

Dr. VARMUS. No.

Mr. SHAYS. OK. I would like to be clear on—just very quickly. Not a lot of time on this. But the nutrition conditions of an individual overseas, malnutrition, other issues that are cultural in terms of wealth, does that distort findings making them applicable to the United States? Just go down the line.

Dr. SATCHER. It can definitely. I think there are instances in which the nutritional or status of the participants—and maybe even in the cases that we've been discussing—has impact. Those are the kinds of things that we want to understand better. But there are instances where we think that we can. One—if I could just get back for 1 second to the EZ studies?

Mr. SHAYS. Yes, sir.

Dr. SATCHER. There are many who believe that the differential mortality that was observed in the countries in Senegal and Haiti could well have been related to the nutritional status of the participant. Now, we haven't had enough studies to know, but there are many who think so.

Mr. SHAYS. Fair enough. OK.

Dr. VARMUS. I would just comment that the hope of obtaining a useful and convincing result in studies carried out and in environments that, as you point out, may be affected by a number of other contributing factors like sanitation, can be most effectively pursued with a randomized control trial.

Mr. SHAYS. Private sector—we haven't even gotten into the issue of when the private sector conducts—we haven't focused on it—their own studies, who oversees the ethical conduct of those studies?

Ms. PENDERGAST. The Food and Drug Administration does, sir.

Mr. SHAYS. So basically you're the operative force in those areas?

Ms. PENDERGAST. Yes. For products that the FDA regulates, we do.

Mr. SHAYS. OK. CDC doesn't get involved, Institutes of Health don't get involved unless——

Dr. VARMUS. We do if there is a collaboration with an NIH supported institution.

Mr. SHAYS. OK.

Dr. SATCHER. Same with the CDC.

Mr. SHAYS. HHS? Through FDA.

Mr. RAUB. Through FDA or, as Dr. Varmus and Dr. Satcher indicated, when there is a collaborative arrangement with work funded by them.

Mr. SHAYS. OK. Dr. Varmus, why don't we let you get on your way so you have some time to get there at 1 p.m.

Dr. VARMUS. I appreciate it.

Mr. SHAYS. And we're going to end in just a few minutes, but let me just pursue this. Ms. Pendergast, Dr. Satcher and Dr. Raub, if you could just participate in this last part. How does the process work in the private sector in terms of informed consent? Tell me how the process would work, the oversight process of FDA.

Ms. PENDERGAST. The——

Mr. SHAYS. In other words, I'm looking for—you don't have a board. Do you have a separate board that oversees the informed consent issue? Who deals with that issue?

Ms. PENDERGAST. The system is very parallel to what governs Federal research. Before a study can be conducted in the United States, the company has to seek the FDA's approval of the trial. The informed consent, and making sure that the trial is ethical, and that the risks are outweighed by the benefits is, again, handled by an institutional review board, which has to be a diverse group of people who will review this study. So you have overlapping responsibilities with the sponsor of the trial who has to make sure that the trial is properly designed and that the clinical investigators are competent.

The clinical investigator is obliged to get informed consent. The institutional review board is obliged to oversee the study and the

consent. And then the FDA has a bioresearch monitoring program where we do inspections of all three: the sponsors, the clinical investigators, and the institutional review boards in an effort to make certain that they are living up to their commitments.

Mr. SHAYS. OK. I'm not quite clear if this is an individual or a board that oversees this process.

Ms. PENDERGAST. With respect to the FDA, we have employees in all of our different centers and across the United States that work on this. We did 1,000 inspections last year with respect to research integrity issues. So there are many people at the FDA involved in this. But every clinical trial has a specific institutional review board at the institution, whether it's a hospital or academic center, that reviews the study before it goes forward as well as the FDA.

Mr. SHAYS. Are there any questions that you wish we had asked that you were prepared to answer, that you would like to answer? Ask the question and answer it; something you feel we should have asked?

Dr. SATCHER. I just want to say that, if we haven't said it before, that I think this discussion is very important, and despite our defense of what we do we understand that these issues require a lot more discussion and debate continually. And I think that's what's going to get us where we want to be in terms of protecting the rights of people in this country and throughout the world. So we appreciate the discussion, and we plan to continue to participate in it, here and outside.

Mr. SHAYS. Doctor, I thank you. This is something that this subcommittee—we have extraordinary oversight because we oversee five departments. And HHS is so gigantic as the Department has a larger budget than most gross domestic products of other countries. So how HHS puts everything together and is able to fulfill its mandate is quite something. We have always tried not to take pot shots at any of you in this business.

We know that we have not always provided the resources for you to do the job, and there is so much that needs to be done. The one thing that we've always liked is candidness. And we're not trying to dig people into holes and then have them climb out. I just want to know, Ms. Pendergast, if you have any comment you want to make, any question you wish we asked or any qualifying statement on anything that you said?

Ms. PENDERGAST. Thank you. I think it's important to recognize that we share your basic concern that the troops during the Persian Gulf conflict were not given the information that we had hoped they would get. Perhaps I was too bureaucratic in my response. We were disappointed. We let the Defense Department know that. And we will submit for the record the precise documents, where they made the promises and our responses back so that you can see what the agency did back then. But I think it's fair to say that that experience taught us a lot. And we will not move forward with other kinds of waivers of informed consent in

the military until there has been another round of public discussion, rulemaking, where we take into account the views of the veterans, take into account all that we learned as a result of this effort, and take into account the concerns raised by the Presidential Commission on the Gulf War. We learned a lot, and we will use that information as we go forward.

[The information referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 30 1997

The Honorable Christopher Shays
Chairman, Subcommittee on Human Resources
and Intergovernmental Relations
Committee on Government Reform and Oversight
U.S. House of Representatives
Washington, D.C. 20515-6143

Dear Mr. Chairman:

As per your request, enclosed please find copies of correspondence between the Food and Drug Administration (FDA) and the Department of Defense related to the waiver of informed consent for the use of Pyridostigmine Bromide during the Gulf War.

We are submitting these documents for the record of the May 8 hearing.

If you have any questions, please let us know.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

Enclosure

cc: The Honorable Edolphus Towns
Ranking Minority Member
Subcommittee on Human Resources
and Intergovernmental Relations

Index of Documents Between FDA/DOD Related to PB/Waiver of Informed Consent

May 1, 1987	MOU - signed by Frank Young, M.D., Ph.D., Commissioner of Food and Drugs and William Mayer, M.D., Assistant Secretary of Defense for Health Affairs, DOD
August 30, 1990	Memo of Meeting between FDA/DOD
September 7, 1990	Memo of Meeting between FDA/DOD
October 30, 1990	Letter from Enrique Mendez, Jr., M.D., DOD to James Mason, M.D. Assistant Secretary for Health, HHS
October 31, 1990	Letter from Martha Myers, Acting Chief, Human Use Review and Regulatory Affairs, DOD to Director, Division of Neuropharmacological Drug Products, FDA
December 11, 1990	Letter from Paul Leber, M.D., Director, Division of Neuropharmacological Drug Products, FDA to Ronald Clawson, Ph.D., Office of the Surgeon General, Human Use Review and Regulatory Affairs, DOD
December 31, 1990	Letter from Gregory Berezuk, Lieutenant Colonel, Medical Service Corps, Human Use Review and Regulatory Affairs Office, DOD to Division of Neuropharmacological Drug Products, FDA
January 4, 1991	Letter from Brian Schuster, M.D., F.A.C.P., Colonel, Medical Corps Director of Experimental Therapeutics, DOD to David Kessler, M.D., Commissioner of Food and Drugs, FDA
January 8, 1991	Letter from Gregory Berezuk, Lieutenant Colonel, Medical Service Corps, Human Use Review and Regulatory Affairs Office, DOD to Stuart Nightengale, M.D., Associate Commissioner for Health Affairs, FDA
January 8, 1991	Letter from David Kessler, M.D., Commissioner of Food and Drugs, FDA to Enrique Mendez, Jr., M.D., Assistant Secretary for Defense, Health Affairs, DOD
January 17, 1991	Letter from Gregory Berezuk, Lieutenant Colonel, Medical Service Corps, Chief, Human Use Review and Regulatory Affairs Office, DOD to Director, Division of Neuropharmacological Drug Products, FDA (This is a subset of the entire submission)

March 15, 1991	Letter from Enrique Mendez, Jr., M.D., Assistant Secretary for Defense, Health Affairs, DOD to David Kessler, M.D., Commissioner of Food and Drugs, FDA
April 4, 1991	Letter from Gregory Berezuk, Lieutenant Colonel, Medical Service Corps, Chief, Human Use Review and Regulatory Affairs Office, DOD to Stuart Nightengale, M.D., Associate Commissioner for Health Affairs, FDA
September 20, 1991	Letter from Paul Leber, M.D., Director, Division of Neuropharmacological Drug Products, to Ronald Clawson, Ph.D., Office of the Surgeon General, Human Use Review and Regulatory Affairs, DOD
November 27, 1991	Letter from Enrique Mendez, M.D., Assistant Secretary for Defense, Health Affairs, DOD to James Mason, Assistant Secretary for Health, HHS
May 27, 1992	Letter from Gregory Berezuk, Lieutenant Colonel, Medical Service Corps, Chief, Human Use Review and Regulatory Affairs Office, DOD to Director, Division of Neuropharmacological Drug Products, FDA
July 24, 1992	Minutes of Meeting between FDA/DOD and Preparatory materials
September 24, 1993	Letter from Edward D. Martin, M.D., Acting Assistant Secretary of Defense, DOD to David Kessler, M.D., Commissioner of Food and Drugs, FDA
July 11, 1994	Letter from Paul Leber, M.D., Director, Division of Neuropharmacological Drug Products, to Ronald Clawson, Ph.D., Office of the Surgeon General, Human Use Review and Regulatory Affairs, DOD
July 27, 1994	Letter from Dale Vander Hamm, MAJ, MS, Chief, Human Use Review and Regulatory Affairs Division, DOD to Paul Leber, M.D., Director, Division of Neuropharmacological Drug Products, (This is a subset of the entire submission)
September 9, 1994	Letter from Dale Vander Hamm, MAJ, MS, Chief, Human Use Review and Regulatory Affairs Division, DOD to Director, Division of Neuropharmacological Drug Products, FDA
September 29, 1994	Letter from Dale Vander Hamm, MAJ, MS, Chief, Human Use Review

	and Regulatory Affairs Division, DOD to Paul Leber, M.D., Director, Division of Neuropharmacological Drug Products, FDA
September 30, 1994	Letter from Dale Vander Hamm, MAJ, MS, Chief, Human Use Review and Regulatory Affairs Division, DOD to Paul Leber , M.D., Director, Division of Neuropharmacological Drug Products, FDA
October 24, 1994	Memo of Meeting between FDA/DOD and Preparatory materials
October 27, 1994	Letter from Dale Vander Hamm, MAJ, MS, Chief, Human Use Review and Regulatory Affairs Division, DOD, to Paul Leber, M.D., Director, Division of Neuropharmacological Drug Products, FDA
November 3, 1994	Letter from Paul Leber, M.D., Director, Division of Neuropharmacological Drug Products, FDA to Ronald Clawson, Ph.D., Office of the Surgeon General, Human Use Review and Regulatory Affairs, DOD
January 23, 1996	Letter from Dale Vander Hamm, MAJ, MS, Chief, Human Use Review and Regulatory Affairs Division, DOD, to Director, Division of Neuropharmacological Drug Products, FDA
May 7, 1996	Citizen's Petition
June 12, 1996	Letter from Dale Vander Hamm, MAJ, MS, Chief, Human Use Review and Regulatory Affairs Division, DOD to Director, Division of Neuropharmacological Drug Products, FDA
September 13, 1996	Letter from Stephen Joseph, M.D., M.P.H, DOD to David Kessler, M.D., Commissioner of Food and Drugs, FDA
October 11, 1996	Letter from Mary Pendergast, Deputy Commissioner/Senior Advisor to the Commissioner, FDA to Ronald Clawson, Ph.D., Office of the Surgeon General, Human Use Review and Regulatory Affairs, DOD
April 16, 1997	Letter from Paul Leber, M.D., Director, Division of Neuropharmacological Drug Products, FDA to Ronald Clawson, Ph.D., Office of the Surgeon General, Human Use Review and Regulatory Affairs, DOD
May 13, 1997	Letter from Russ Zajtchuk, Brigadier General, Medical Corps Commander, DOD to Director, Division of Neuropharmacological Drug Products, FDA

Mr. SHAYS. I appreciate that comment. Let me just say it's not meant to be an aggressive statement on my part, but words like "hoped" and "disappointed"—it's not that we want the hope that they do it—and the mere fact that that word is still being used—and I'm not trying to nit-pick here. I just think that what we will probably, as a subcommittee, give you plenty of warning before we have a hearing just on the whole issue of what the military was supposed to do with the waiver, and how they responded and then how you responded.

And I'm hopeful that maybe that hearing won't be necessary. We'll look at what you have given us. But I'm going to just suggest it. It may be what will be required to have it publicly understood how strongly you feel about it and how strongly Congress feels about it as well, so that it will be an added incentive for the people that take your place. Because, God help us, we won't have this kind of need for many years in the future, if ever. Any other comments that others might want to make? Yes, sir.

Mr. RAUB. Mr. Chairman, just the comment of thanks to you for focusing on these issues. In particular, the notion of having some continuing mechanism to address ethical issues has not always received a lot of attention, its significance not always understood. I believe your hearings have sharpened those questions and provided an important set of information.

Mr. SHAYS. Well, I thank you. I have to say that as I talked about a permanent advisory board, I was thinking, there you go again. You say you want to reduce the size of Government, and you want something permanent. So I acknowledge that in this area I think that there needs to be something a bit more permanent. And maybe I'm wrong and maybe I'll reconsider. But I will look forward to the dialog that we'll have. It's always been a constructive dialog with the FDA, the Institutes of Health, HHS, and CDC. We've really always appreciated the cooperation we've received and the staff has received.

I thank you all, and I thank all those of you who were sworn in who never got to testify. I really frankly probably would have learned more from all of you. I just wish I knew that question that would have triggered you to come forward. Thank you, and we'll hear the next panel. Thank you all.

Ms. PENDERGAST. Thank you.

Mr. SHAYS. This committee will call forward Arthur Caplan, professor of bioethics, University of Pennsylvania, Benjamin Wilfond, who is professor of pediatrics, University of Arizona; Dr. Peter Lurie, professor of medicine, University of California; and Laurie Flynn, executive director, National Alliance for the Mentally Ill.

So we will proceed in the order of Dr. Caplan, Dr. Wilfond, Dr. Lurie, and then Ms. Flynn. Do we have all of the witnesses here? And I'm going to catch you before you sit down, Ms. Flynn, because we're going to have everybody stand and I'll swear you in.

[Witnesses sworn.]

Mr. SHAYS. Thank you. For the record, we had five who stood up and four witnesses who will actually testify. And all responded in the affirmative. I'm sorry. We have a vote. I've gotten you sworn in; that's one task. We have a 15-minute vote and a 5-minute vote. So I will say that it's unlikely that we will be back until 1:30 p.m.

And I'm sorry about that. I will say before we recess that I am very grateful to the four of you for coming to testify and listening to the first panel, and will welcome your response and observations of what you've heard from the first panel. So you can digress a bit from your statement to also include comments about that. And we will recess. And given the vote, we will probably not be here until 1:30 p.m.

[Recess.]

Mr. SHAYS. This hearing is called to order. Do any of you have plans for this evening? I think, Dr. Caplan, we're going to begin with you. And welcome.

STATEMENTS OF ARTHUR CAPLAN, PROFESSOR OF BIOETHICS, UNIVERSITY OF PENNSYLVANIA; BENJAMIN WILFOND, PROFESSOR OF PEDIATRICS, UNIVERSITY OF ARIZONA; PETER LURIE, PROFESSOR OF MEDICINE, UNIVERSITY OF CALIFORNIA-SAN FRANCISCO; AND LAURIE FLYNN, DIRECTOR, NATIONAL ALLIANCE FOR THE MENTALLY ILL

Mr. CAPLAN. Thank you, Mr. Chairman. I'm very pleased to have the chance to testify before you and the committee. The question of whether the time has come to consider changes in the way Americans are recruited to and participate in biomedical research is of obvious importance, as we've heard some of the issues discussed this morning. I think research is very crucial to the high level of care Americans receive and that is available to them. But it also does require the participation, the sacrifice and even the voluntary altruism of people who are going to be subjects.

And so protecting their interests and their rights is crucial in order for continuing progress to be made in the quality of care we receive. It seems to me that this Nation has not always done what it ought to do to ensure the welfare and dignity of those who make themselves available as subjects. We've heard reference already this morning to incidents in our own past—the Tuskegee study and some of the exploitation of people in the military in the 1950's and 60's involved in radiation experiments, mentally retarded children.

So we know we have to do better. We have to be vigilant. And at the same time I think we've tried to institute a series of protections—informed consent and peer review by IRBs—that will keep us away from some of our most egregious failures in the past. Really what I want to do is talk just a bit. You have my written statement. So I'd like to just concentrate on a few areas where I think those two protections are in jeopardy. We've heard a lot today about one of the areas that I want to especially focus in on.

That is the IRB system. I've been on IRBs for a long time. I have chaired a number of IRBs at different institutions. I think I have a very good understanding of what IRBs—institutional review boards—can do. And their charge, in part, is to make sure that people do get informed consent by looking at the informed consent forms, by weighing risk and benefit that is put before them. But Mr. Chairman, I think there are a number of factors in the research world as we now know it that are impairing the ability of the IRBs to do their jobs.

We've had reference briefly to the phenomena of privatization of research funding. More and more of our research is now supported

by private sources, not the NIH and not Federal sources. We find ourselves in situations where private sources are beginning to put restrictions on information that is available to not only subjects but to IRBs.

And in this area in particular I'd like to note for the Chair that we've had incidents where private companies have now stepped forward and said research cannot be published because it is held as a secret or that it has been contracted with an institution, that it will be done with condition that the company must sign off. A recent example of this was Boots, now the Knoll Pharmaceutical Co., with its drug Synthroid—is one such example of restriction of information.

Mr. Chairman, if an IRB cannot get all the information that it needs to have about conflict of interest, financial sources of funding, if a firm is in a position to say that it will not publish legitimate findings about a particular drug or device, then the interest of subjects cannot be protected. So if we need to—and I feel we must—we have to ensure that IRBs have the information available to them so they can know when a researcher has a conflict of interest. We need to make sure that secrecy and provisions of restriction on findings of information are not part of what goes on in American institutions. In the end, to fail to publish findings—and I say this knowingly and deliberately—but to fail to publish findings that you have is a betrayal of what is owed to human subjects. If you don't get results out, if you don't put them in the peer reviewed literature, then you've asked people to carry burden, be involved in risk, face a sacrifice in coming to and from experimentation, for no purpose.

And so for me, one of the most sad and unfortunate consequences of what we're asking our IRBs to do is we're asking them to work sometimes without the information, without the access that they need to have to do the job right.

That makes me cite a secondary issue, which I think the chair should pay close attention to. I'm very impressed with the previous panel and its comments about the role of IRBs and making sure that informed consent forms are understandable and that people have information.

But Mr. Chairman, I feel we have a system now that is spending too much time at the front end of research, looking at the written informed consent forms—that's what IRBs do. And the ones that I've served on—I would estimate that 97 to 99 percent of the time is spent in a room looking at an informed consent form, trying to translate medical jargon back to English. Sometimes that works and sometimes it doesn't. Sometimes subjects know more than you think because they've been involved with the disease process and have learned a lot about medical issues. So what looks difficult to understand to the outsider may be understandable to those subjects.

But where the system is not doing its job is in monitoring and making sure that what is on that form is actually taking place in the research setting. Very rarely do IRBs spend any time talking to subjects. Very rarely do they debrief anybody. Very rarely, if ever, do they find themselves in contact with researchers, actually going out and saying, did you sign this form, did you understand

this form, is it capturing the things that turned out to have been of interest and concern to you as you were a subject in research?

In other words, the feedback loop that ought to be there between actual subjects and actual research, and what goes on in practice, and what you see at the front end when someone says, here is what I propose to do, and here is what the form is to accompany it, is broken. It is simply broken. And we have to do something to restore that loop of information so that when an IRB is taking a look at a research protocol it can say, we've been out and talked to some of these subjects, we know that the researchers are doing what they told us they would do.

We need more audit. We need more oversight. We need to get more time available for IRB members to spend talking with subjects. In this era—and I'm just going to make two more points and then I'll stop in the interest of time—in the era of IRB and informed consent work, there's something else that's missing, Mr. Chairman.

If you were to ask any of the officials who were with us in the previous panel, tell me; who is in research? What is the composition in America of who participates? What are the statistics about who is involved in the military? From the ranks of those with mental disability or mental illness? Minority people? Poor people?

That can't be answered. We have never insisted as a Nation that we collect basic statistics and demographics on who is involved. Are women over or underrepresented? Are the elderly over or underrepresented? Are Native Americans getting the access that they might have? We don't know. There is no data collected. In fact, sadly, incredibly, we collect more standardized data on animal use than we do for people in this country. And it seems to me some of the questions of informed consent, the adequacy of how research proceeds, and fairness and equity and access to research and, how well people are treated, require basic information for answers.

That leads me to the last point I'd like to make. In looking at research and informed consent it is clear to anyone who wants to look out here—and you've talked about some of this this morning already, and I have to confess given the tone of direction of some questions, I'm on that Presidential Advisory Committee for Gulf War Illnesses, and the interest of research in the military has been of special concern to me as a member of that committee. But, I have to tell you, Mr. Chairman, that for our vulnerable populations—people who are impaired or unable to consent on their own for reasons of age or mental disability or institutional settings like a prison or service in the Army or even being a student, a medical student dare I say—it is clear that informed consent has its limits, that there are just people out there who want to be in research, who want the opportunity to be in research, who, one way or other, are not going to be able to give a full informed consent to their participation in research.

We have not yet, I think written the regulations and put the kind of oversight in that would help those people. I'm sorry to tell you, Mr. Chairman, I don't think we have a policy today that is any different from what we had in 1990 prior to the Gulf war about research in the military. I think the issue could arise tomorrow as to what could or couldn't be done with soldiers or sailors or people

in the armed forces with respect to research and who would approve that and how that would proceed. We are operating with an interim, temporary rule in that area right now. We have been for 6 years.

And it seems to me we ought to fix that. When we look at issues involving research with the mentally ill or people who are institutionalized with Alzheimer's and see the number of problems and scandals and difficult cases that have arisen—at UCLA, the Medical College of Georgia—there are many, many settings where people have, I would say, been taken advantage of or not understood what is happening to them in terms of recruitment to research. The time has come, I think, to toughen those regulations and perhaps to add more than just IRB oversight. It may be time to say that we need to have some national or regional review of certain kinds of high risk groups involved in research and certain types of high risk research itself, that local IRB review may not be enough.

So Mr. Chairman, in summary, I think that the system we've got is better than what we once had, but it hasn't been much changed since 1981. That's the last time the rules of informed consent and IRB review got a thorough going over. I think it's overdue. I think there are some concrete steps that could be taken to toughen those regulations and afford better protection to those who make the gift of themselves to participate in research so that they and others may benefit.

[The prepared statement of Mr. Caplan follows:]

Mr. Chairman and distinguished subcommittee members, I am very grateful for the opportunity to testify before this committee. The question of whether the time has come to consider changes in the way Americans are recruited to and participate in biomedical research is of obvious importance. This hearing is an especially important one since recent scientific advances continue to demonstrate the value of research with human subjects. Research is crucial to the high level of care that Americans can receive in our health system. However, research also requires the participation of subjects if progress is to continue to be made. Thus, it is essential that Congress remain vigilant with respect to the adequacy of the protections afforded those involved as subjects in biomedical research.

This nation has not always done what it should to insure the welfare and dignity of those who altruistically make themselves available as subjects so that medicine can learn and advance in the battle against disease and disability. As the troubling revelations of the exploitation of subjects including children with mental retardation, the elderly and soldiers in the 1950s and 1960s in research involving the study of radioactive substances and the outright deception and fraud perpetrated by our government upon poor African American men infected with syphilis in rural Alabama for four decades in the notorious Tuskegee study, this nation's ethics have not always been what they ought to have been in the area of biomedical research.

As a result of these and other scandals coming to light, a debate ensued in this nation concerning the ethics of human experimentation. In the past two decades we have as a society made a commitment to do better to those involved in research as subjects. And we have.

In my view our current system of laws, regulations and teaching programs insures more protection of the rights and welfare of those involved in human research than exists anywhere else in the world.

Still, Congressman Shays, I believe that still more can be done. It is time to revisit the adequacy of human subjects regulation in the United States for three reasons; a rapidly changing research environment that casts doubt on the adequacy of informed consent and IRB review, a lack of basic information about who is involved in research and inadequate attention to the needs of those who are most vulnerable in research contexts. These reasons provide both a basis for a reexamination of human research ethics and for some recommendations I wish to offer this committee about reforms and changes that might help stregthen our existing protections of informed consent and peer review by IRBs to meet the moral challenges that have already and will continue to appear in biomedicine.

Shifts in Financing, Organization and Purposes of Human Research

For thirty years research in the United States has been subject to policies and regulations imposed by the Federal government. In the wake of scandals in the late 1960s and early 1970s such as the Tuskegee syphilis Study, the Brooklyn Chronic Disease Hospital cancer study, and the Willowbrook hepatitis vaccine trials two sets of protections were created for those recruited to serve as subjects in biomedical research. The first, informed consent, requires that participation in research be voluntary, informed and freely chosen. The second, review by local institutional review boards (IRBs), insures that the scientific merit, risk/benefit ratio and informed consent documents associated with individual research proposals are approved by the peers

of those seeking permission to undertaken research. Local review with relatively little centralized oversight by Federal agencies of recruitment and consent practices was held to be most consistent with American values, easier to implement and most responsive to the style of Federally sponsored, project and researcher oriented funding that characterized biomedical inquiry in this country in the 1970s and early 1980s.

The twin protections of informed consent and IRB review have served subjects well. Some of the most egregious scandals in our own history of research involving human subjects; such as the racism, deception and callous indifference to human life of the Tuskegee study, could not take place under the current system of regulation. However, the existing system of regulations has not been revised or revisited in any serious way since 1981. In the more than a decade and a half since the rules were last revised a number of changes have occurred in the conduct, organization and financing of human research.

Privatization

One of the most startling changes has been the shift from public to private sources in the funding of human subject research. Private industry is now the major source of funding for biomedical research in the U.S. Since 1980, industry's share of U.S. biomedical research and development rose from 31% to 46%, while NIH's share dropped from 40 to 32%. The dramatic increase of industry funding of biotechnology and clinical research is reflected in university research budgets as well. Industry support of all university research has nearly doubled in the last decade from 4 % to 7%. More than a third of the authors of a recent sample of leading biomedical journals had at least one potential conflict of interest as a result of receiving private support or holding a financial interest in the drug or device being studied.

Privatization in support for biomedical research has led to some obvious problems and challenges. Let me comment on a few of the most imprint of these.

Access to information for subjects, researchers and the public is emerging as a problem. More secrecy is being introduced in research protocols as a result of the fact that commercial motives are fueling the content and direction of an increasing number of biomedical research projects. As the recent contretemps between the University of California, San Francisco, and the Knoll Pharmaceutical Company (formerly Boots Co.) illustrates private concerns can and do exercise control over what researchers can publish. When a UCSF researcher found that a widely used drug Synthroid, which costs Americans $600 million per year, was biologically equivalent to the much less expensive generics the company suppressed publication of the findings and threatened UCSF with a lawsuit to keep the study from being published.

The privatization of research has led to another shift in human subjects research. Private concerns frequently seek subjects in order to test new drugs or devices they wish to bring to the marketplace. Federally funded research was far less likely to be driven by commercial considerations than is privately sponsored research. This means that human subjects may be asked to carry risks or face the burdens of participation in a research trial not fully understanding that the research is being undertaken with a commercial purpose in mind. I have seen many protocols come before IRBs on which I have served over the past few years where the drug which was to be tested was being tested so that a particular pharmaceutical firm could enter into a lucrative market where many other similar or nearly identical drugs already existed. Subjects may not be informed of the fact that the researcher requesting their participation in a study stands to gain

financially from their consent. Nor do they always understand why a study is being done or what will be done with the results of a study sponsored by a private concern.

The shift toward more private rather than public support of research raises questions about the adequacy of local IRB review which plays such a key role in the Federal oversight of human research. IRBs may not always know what the conflicts of interest are that exist due to ties between researchers and private funding sources. They may themselves be in a conflicted position, trying to do the right thing by those who are subjects but feeling tremendous pressure not to alienate those who provide the bulk of support for a particular center or department within an institution. Indeed, some forms of research, when conducted entirely with private support, may not fall under the legal aegis of IRB review.

The privatization of research has been accompanied by another major change in the nature of biomedical research. The era of the single investigator conducting work with a set of subjects at one institution is coming to an end.

Multiple Investigators at Multiple Locations Imperils informed consent and strains IRBs

Today, many subjects in research participate in 'multi-site' studies. These are studies that involve many investigators recruiting subjects at many different institutions and locations, often across national boundaries. Multi-site research was not the model that shaped the creation of local IRBs as the lynchpin of peer review for approving human research. And it is becoming increasingly obvious that local IRBs cannot handle some of the issues that arise in public and privately funded multi-site research. One such example

is the large scale misconduct which in 1994 cast suspicion over the integrity of the National Surgical Adjuvant Breast and Bowel Project (NSABP), the single most important source of information women facing surgery for breast cancer have available for themselves and their doctors.

Dr. Roger Poisson of St. Luc hospital in Montreal fraudulently enrolled at least 100 subjects into this study. His patients constituted 16% of the study population. Researchers in this multi-center study were paid on the basis of the number of patients enrolled. High subject recruiters such as Poisson were also given authorship on key papers from the NSABP.

None of the fraud which occurred in this study was detected and reported by any IRB. In fact, there were tremendous variations in the informed consent forms used by participating institutions to recruit subjects. And no IRB member was ever asked to audit or debrief any subject or investigator in the study at any point during the many years it ran.

Multi-site research poses real challenges for the current system. Local IRBs may or may not be coordinating their review of informed consent documents. Investigators conducting the same study at different places must often contend with inconsistent demands and requests by IRBs. And subjects may not receive a core or minimal set of information about a study for which they are being recruited depending on the zealousness and competency of the IRB. Indeed, some research is conducted under the auspices of IRBs that are hired for the sole purpose of reviewing studies, raising questions about their ability to assess and monitor local conditions and the needs of particular subjects for information or special protections in particular places.

A Lack of Basic Information

This is not at all unusual. IRBs lack the manpower, budget or time to do very much more than review written research protocols and check informed consent forms. In my experience I have never met an IRB member who has spent any serious amount of time debriefing subjects or visiting with researchers was approval to conduct research with human subjects has begun to assess the nature of the ethical problems that have actually arisen in the course of the research. IRBs are trapped by paperwork. They almost never talk with researchers or subjects. Thus, they remain uninformed about the extent to which what they require on paper in the way of informed consent is actually put into practice or valued by the subjects of that research.

Compounding the burden IRBs face is the fact that there is no systematic data collection about the demographics of participation in human research. We mandate far more stringent data collection and monitoring regarding animal subjects than we do human subjects. No one can say what the workload is that IRBs face, what the demographics are of those asked to participate in research, or what the actual demographic content is of those volunteering to be in research in any given month or year because no data about any of these matters is systematically collected or published. If there are trends involving the participation of women, poor people, the mentally ill or Native Americans or any other group because no historical data exists about demographics or the nature of those involved in human research.

Nor is there any systematic debriefing done of those who have participated in research or who have acted as surrogates for those not competent to consent for themselves. This means that IRBs must operate in a vacuum when issues of discrimination, fair access or bias arise with respect to

research protocols. It also means that there is no way to check whether IRBs actually do emphasize in their work the kinds of issues that are most important to those who actually serve as human subjects.

Nor is there any systematic data collected on IRB performance. Audits of IRBs are rare and usually triggered by the hint or allegation of a problem. The ability of IRB members to monitor the actual conduct of research and their skill in doing so is not demonstrable by existing means of oversight of the IRB system. Many subject remain unaware of what to do if they feel they have been mistreated or wronged in the course of research. And by having the major Federal office responsible for the protection of research subjects, the OPRR, located at the NIH it may not be possible for that agency to have the kind of independence and autonomy necessary to monitor both private and publicly sponsored research activities.

The Failure to Grapple with the Needs of Vulnerable Populations in Human Research

For many years it has been well understood that not all subjects in human research can look out for their own interests. When people are, for various reasons, incapable of fulfilling exercising their power of self-determination, of acting as an autonomous agent, they are at increased risk in serving as a subject because one of the two forms of protection deemed crucial for ethical experimentation, informed consent, is not available to them. Classic examples of such vulnerable subjects are children and fetuses. Special regulations govern their participation in research since they are unable to consent to participate for themselves.

In recent years a series of problems and scandals have arisen with some populations of persons involved in research. These include the severely mentally ill, members of our armed forces, the senile elderly, the terminally ill, students and those who become suddenly and unexpectedly acutely ill. There is also a very important issue of the extent to which our guidelines concerning informed consent will be followed when research done by Americans or sponsored by American companies or government agencies is done outside our borders. Many of the subjects in studies in poor nations lack the education and even the cultural familiarity with concepts like autonomy and individual rights that would allow them to make full use of informed consent.

Experiments have been conducted on persons with mental illness where informed consent has been poor and the monitoring of subjects involved in studies inadequate. Complaints by a number of persons afflicted with schizophrenia and their families about studies carried out at UCLA raise some very though questions about the adequacy of existing rules for protecting those made vulnerable by mental illness. Issues have arisen concerning the rights and duties those serving the nation on active military service have in times of war and peace with respect to participation in biomedical research undertaken for military purposes. Some of those who served in the Persian Gulf conflict were exposed to vaccines and drugs under circumstances that closely resemble research with no informed consent. Patients with dementia are routinely recruited as subjects in studies while residing in institutional settings where their ability to consent may be greatly impaired or where it is not clear who ought act as their surrogate decision-maker when they are obviously unable to consent. And terminally ill persons have been subject to all manner of innovative efforts at clinical therapy, such as to give one of many, many such examples, the newly emerging surgical procedure for treating heart failure

sometimes known as the Batista procedure, with no review by IRBs because there is no clear-cut requirement that new and innovative procedures be subject to any level of review on a par with what must be done before a subject can be involved in the testing of a new drug or medical device. Recently, this nation has been shocked by revelations of efforts to pioneer new forms of organ procurement protocols whose sole source of approval is the local IRB of the institution seeking to increase the supply of donors.

Those who cannot consent or who can do so only in a limited sense, still deserve the opportunity to participate in biomedical research. There are often benefits to be gained from participation in research, both direct for the subject and indirect in terms of knowledge gained that can benefit others with similar conditions and debilities. Vulnerability is not in itself a sufficient reason to deny participation in research to any person. But, there is sufficient evidence available to conclude that some groups, such as the mentally ill, the institutionalized demented elderly and those in military service, require more protection then they are currently being afforded by existing regulations, while others such as children, the terminally ill and the unexpectedly acutely ill may need more protec
tion then they are currently being afforded by a system of local IRB review.

Recommendations

There are many areas where Congress might legitimately call for greater action on the part of Federal agencies and offices responsible for protecting the rights and welfare of human subjects in biomedical research. I am going to conclude my statement with seven suggestions which I believe are the most deserving of attention and action.

1. Special provisions for those with cognitive and emotional impairment sufficient to interfere with the capacity for informed consent should be added to existing regulations governing human subjects research.

2. A clearer defintion of research should be incorporated into existing Federal regulations so as to insure that what is truly and obviously new, innovative and pioneering is subject to consent and IRB review.

3. Steps should be taken to decrease the paperwork burden faced by researchers and IRBs and to permit IRBs more time to conduct monitoring activities of research and to debrief subjects. This could be accomplished by moving the current review system in the direction of random audit along the lines used by the IRS, FDA and many commercial enterprises to insure quality control.

4. Standardized data on human subject participation in research as well as IRB activity should be mandated, collected and made widely available.

5. All sources of conflict of interest must be disclosed to IRBs and all information necessary for the protection of human subjects must be placed in their hands regardless of commercial concerns.

6. For some categories and kinds of research involving vulnerable populations or high risk inquiry consideration ought be given to the creation of regional or national IRB-like review mechanisms to be added to local IRB review.

7. More audit and monitoring responsibilities should be given both to local IRBs to assess compliance with informed consent and to the OPRR at the NIH to monitor IRB performance.

Mr. SHAYS. Thank you very much. And I guess we are going next to Dr. Wilfond.

Dr. WILFOND. I thank you, Mr. Chairman.

Mr. SHAYS. I didn't say your name well, so when you heard me say it, you wondered who the heck is he talking about. Is it Wilfond?

Dr. WILFOND. Wilfond.

Mr. SHAYS. Thank you, Dr. Wilfond.

Dr. WILFOND. I'd like to thank you for inviting me to participate in this meeting. Currently, I'm an assistant professor of pediatrics in the sections of pediatric pulmonology and medical and molecular genetics at the University of Arizona in Tucson. As a pulmonologist I care for children with cystic fibrosis and asthma as well as other lung disorders. I also teach bioethics, and I'm a member of the American Academy of Pediatrics Bioethics Committee. I've been a member of IRBs for the last 9 years, and I have a particular interest in research issues related to children.

Informed consent has been a central tenet of research ethics since the Nuremberg trials 50 years ago. In fact, as a legacy of the trials, in the 1970's there was great debate whether children ever should be able to participate in research, since they are unable to give their consent. This debate was considered in the Belmont Report and expressed in the Federal regulations by acknowledging that parents give permission and not consent for their children to participate in research.

This distinction is important, although it's subtle. But it provides a conceptual justification for IRBs having a greater role in terms of the review of projects on children. For those studies that involve greater minimal risk, the IRB is to make a normative judgment about whether or not the risks are balanced by the benefits before the parents are able to give the decision to allow their child to participate. I think this is a very good thing, although there still remains a lot of conceptual vagueness in exactly how this is carried out. There is room for a more conceptual work trying to understand even what counts as minimal or a minor increase over minimal risk as a regulation state or considering this review.

Although the regulations tend to be more careful in how research is done on children, often the regulations are misinterpreted and are used as a justification for why research in children is not done on a more routine basis. In fact, as a pediatrician, often because of a lack of research, there are many circumstances in which clinical judgments must be made without the availability of sound clinical data. Additionally, many drugs that are used on children are off label.

In fact, taking care of patients with asthma, there are very few drugs that have been approved by the FDA for the use in children. I don't think, though, this problem is really because of the regulatory mechanisms for research. I actually think that it's more related to the lack of incentives for conducting research on children. Once a new drug is approved, pharmaceutical companies have few incentives to conduct studies in children. And so that there need to be requirements to conduct studies in children concomitantly with those of adults. Because it's better to expose children to the risks of research than to the risks of unscientific practices.

What I'd like to do is talk about what I see as some of the problems with IRBs. What I'd like to do is mention five problems I see, but only will talk in detail about one of them. As was alluded to earlier, there needs to be a better mechanism for the oversight and monitoring of multicenter trials. This is a real challenge for IRBs when they review a study that's being done at 10 different places. And if one IRB has problems there's no opportunity for us to correct those problems at all centers. All we can do is choose whether or not we want to accept or reject the proposal.

As was mentioned before, some research that's done in the private sector does not fall under FDA or NIH purview. And so there can be some research that could be done without the involvement of either oversight institution or organization. But I think more importantly and related to that, there needs to be a single mechanism for oversight of IRBs that includes not only the FDA and NIH but for all research. But what I'd like to do is to talk with you about one particular problem.

Mr. SHAYS. I just missed your point. And it's a very important point.

Dr. WILFOND. OK.

Mr. SHAYS. You said there may not be review by either FDA or——

Dr. WILFOND. If—OK. Certainly any study that involves the use of drugs or investigational devices will come under FDA. Any study that is done with NIH funding will come under the review of NIH. Any study that is done at an institution that has a multiple project assurance from either of those organizations will come under their review. But if——

Mr. SHAYS. Come under their review?

Dr. WILFOND. Come under the review of a local IRB.

Mr. SHAYS. Of a local IRB?

Dr. WILFOND. Right.

Mr. SHAYS. But you're basically telling me that the FDA—the question I had put to FDA was: Who oversees the private sector? And you're suggesting that there's some private sector that they don't oversee.

Dr. WILFOND. If there's research that's being conducted that does not involve an investigational drug or investigational device or even one that's been approved for other purposes, then—for example, nutritional modifications or behavioral issues, that it's being done by somebody——

Mr. SHAYS. Let me just clarify something. I'm making a leap here. My mind is thinking this way.

Dr. WILFOND. Sure.

Mr. SHAYS. If something is not going to the marketplace, are you suggesting that the FDA wouldn't be involved?

Dr. WILFOND. That is correct.

Mr. SHAYS. There are a lot of circumstances where something isn't coming to the marketplace. That isn't being funded. Well, who the heck——

Mr. KUCINICH. Nobody.

Ms. FLYNN. No one.

Mr. CAPLAN. No one.

Dr. WILFOND. But actually, even when it does come under FDA—actually what I'd like to do is talk to you about a particular problem in more detail.

Mr. SHAYS. Do you all have any other little secrets you want to tell me about?

Dr. WILFOND. Well, actually, the next one is the one I want to tell you about in more detail——

Mr. SHAYS. OK.

Dr. WILFOND [continuing]. Which has to do with researchers who are in private practice where they have greater incentives for recruiting patients—and this is a case where the IRB mechanism is very different, and essentially are for-profit IRBs. Let me try to explain what I mean by that. Recently at the University of Arizona, we reviewed a study for a new anti-inflammatory treatment for childhood asthma.

Mr. SHAYS. Don't feel you have to read so quickly. You can slow down a bit.

Dr. WILFOND. OK.

Mr. SHAYS. OK.

Dr. WILFOND. We reviewed the study for a new treatment for asthma. The study involved putting patients either on this new anti-inflammatory treatment or a placebo. The problem is that there already are currently available good treatments—anti-inflammatory treatments for asthma. When our IRB looked at this proposal we said this is unethical to do because it denies half of the patients a known effective therapy.

Even with the permission or consent of the parents we felt that this was unfair and unsafe to expose children to this risk. So this was a multicenter trial. All we could do is say, you can't do it here. Two miles down the road there is a physician in private practice who also was doing the same study. What he did was, he had it reviewed by an IRB in another State, and he paid the IRB to review the study and they approved it.

And so I think there are two problems here. One is the obvious problem of the investigator specifically paying an IRB to review their protocol. But more importantly, this review occurred in another State. And I think it completely subverts the whole notion of an institutional review board. In other words, this person was not from the community. And I think that becomes really a challenging thing. I'm not sure I would agree with this. The way IRBs really work is not only looking at the consent forms but trying to be careful that we understand that the investigators, when they present the information, hopefully will do it in a non-coercive way.

Because we don't really have a good way of monitoring exactly how well they do that. The best we can do is to know about the integrity of the investigators. And I want to give you an example of how this happened with this particular study. When it was submitted to the University of Arizona the patients were going to be paid $250 to participate in the study. Our policy is that if payment is going to be made for children two things must happen. First, it cannot be advertised in newspapers in terms of a dollar amount. Our concern is that parents will see a dollar amount. That may be an incentive for them if they're a little short of cash that month

to have their children enroll in studies. So we exclude dollar amounts.

Second, although money may be paid, it's usually paid in the form of a savings bond that is made out in the name of the child. The physicians in private practice usually will have advertisements with dollar amounts. But often the dollar amounts are much higher than we would have otherwise approved. So for example this one study that we looked at, the dollar amount at the university setting was $250, but at the private sector it was $750 that the parents would be paid. And this is being advertised in local newspapers. I see this as being a very big problem.

You know, in the community setting there is greater financial benefit to the investigator to recruit patients. They have increased promotional activities. The studies themselves may be more risky and they're getting less review. And I think this is really one of the biggest issues I think that needs to be addressed. Because I think more and more research will be happening outside of academic institutions. My recommendation would be that whenever feasible all research be reviewed within the same community and that the same IRB have a jurisdiction over all the particular investigator's protocols. One of the problems that the investigator can mail his protocol to different IRBs. So if he gets turned down at one place he can go somewhere else. And I think there needs to be some way of having some control over that.

Mr. SHAYS. Elaborate a little bit on that.

Dr. WILFOND. OK. For example, if a person is in private practice, and he sends it to IRB A and IRB A turns it down, he could send it to IRB B and have them approve it. There's not one designated IRB—whereas in the university setting, at the University of Arizona, if we don't approve a protocol, that investigator essentially can't do that study.

Mr. SHAYS. If you're not part of the university and you're in the same town as the university, tell me where you would go?

Dr. WILFOND. Wherever you want. Whoever gives you the lowest price. There are IRBs around the country that are essentially commercial IRBs that are set up, where they will receive protocols from investigators who mail in a check and mail in the protocol and they will review it.

Mr. SHAYS. I wish this panel had gone first.

Mr. CAPLAN. It's called IRB shopping, by the way.

Ms. FLYNN. Yes. IRB shopping.

Mr. SHAYS. OK. Keep going.

Dr. WILFOND. That's really the main thing I wanted to say. I think this is the biggest issue. I agree with Art about the issue of monitoring in the future. But I think this is really a problem that needs careful evaluation. I think at this point I'll stop and let the other people go.

[The prepared statement of Dr. Wilfond follows:]

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Benjamin Wilfond MD
University of Arizona
May 8, 1997

I would like to thank the subcommittee for inviting me to participate in these hearings about the adequacy of informed consent for biomedical research. I have been asked to make comments about research on children. I am an Assistant Professor of Pediatrics in the sections of Pediatric Pulmonary and Medical and Molecular Genetics at the University of Arizona in Tucson. I am a member of the Committee of Bioethics of the American Academy of Pediatrics. I teach bioethics, including research issues, to medical students and graduate students. As a pediatric pulmonologist, I care for children with lung disorders, including asthma, cystic fibrosis, and chronic lung disease of prematurity. My main research interests are the ethical and policy implications of new genetic technologies. I have a particular interest in the issues of research in children. I have been a member of Institutional Review Boards (IRB) for nine years.

Informed consent has been a central tenant of research ethics from the time of the Nuremberg trials fifty years ago. However, consent is neither necessary nor sufficient to make research ethical. Had the Nazis obtained consent, it would not have altered our judgment about their medical experiments. As a legacy of Nuremberg, there was great debate in the early seventies as to whether it was morally justified ever to conduct research on children since they cannot give consent. This debate was considered in the Belmont Report and expressed in the federal regulations by acknowledging that parents give *permission*, not *consent*, for children's participation in research. This distinction, while subtle, is important, because it provides the conceptual justification for a greater role of the IRB in assessing the balance of benefits and risks to which children can be exposed.

While the intent of the regulations is to place greater restrictions on research on children, the regulations are often misinterpreted to suggest that research that otherwise might be valuable cannot be done. In fact, as a pediatrician, there are many circumstances where clinical judgments must be made without the benefit of sound empirical data. Additionally, many drugs that are used in children are off-label. This problem is not necessarily the result of regulatory restrictions but often, as a result of decisions to not expend the resources to conduct studies in children. Once a new drug is approved, pharmaceutical companies have few incentives to conduct other studies in children. There

need be requirements to conduct studies in children concomitantly with those in adults. It is better to expose children to the risks of research than the risks of unscientific clinical practice.

Conceptual vagueness of the regulations. Let me turn to the federal regulations, as this will provide a framework for understanding some of the remaining problems for the participation of children in research. The regulations stipulate that if research is not greater than minimal risk, then the permission of the parent and the assent of the child, to the extent capable, is sufficient. There are two issues to note. First is the acknowledgment that depending on their maturity level, children should have a greater role in the decision to participate in research. More conceptual work may be needed to flesh out how this should work operationally.

The second point is that if studies involve greater than minimal risk, the IRB is to make a normative decision that the potential risks are balanced by the benefits of the study, prior to parents being given the option of permitting their children to participate. The IRB should attempt to "track those decisions that would be made by informed and scrupulous parents."

The threshold criteria for IRBs to make this moral assessment is "minimal risk", defined as "the magnitude and probability of harms or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (45 CFR 46.102 (I)). There has been great attention to this definition of minimal risk, with no clear consensus. For example, even though a risk of everyday life for a child might include a bicycle accident, it wouldn't justify a study involving children riding bikes in heavy traffic.

If the risk is greater than minimal, the regulations provide the IRB with different necessary criteria, depending upon whether the research offers the prospect of direct benefit to the child. If there is a prospect of direct benefit, then two additional criteria must be determined by the IRB. First, the risk must be justified by the anticipated benefit, and second the relationship between benefits and risks must at least be as favorable as other alternatives. The regulations are not clear about whether studies with placebos should fall under this category of direct benefit. In placebo controlled studies, it is possible that a child will not benefit because the study drug is no better than placebo, or because they have received the placebo. Yet the study offers the prospect of direct benefit, even though not all children in the study will benefit. This points to one of the potential problems with informed consent for studies of direct benefit; the tendency of investigators to overstate the benefits of participation. Even with review of the consent form by an IRB, it is possible

that parents assume that their child will benefit. This could pose a problem when children face life threatening diseases.

If the research does not offer the prospect of direct benefit, it must be likely to yield generalizable knowledge about the subject's disorder. This tends to limit research to issues directly related to children. In addition to the usual requirement for parental permission (which is based on the parent's own assessment of benefit and risk), the IRB must make its own assessment based on the following features.

First, the "generalizable knowledge must be of *vital* importance to understanding the child's disease." While "vital" is not defined, it suggests the IRB must make a judgment regarding the scientific merit of a proposed study.

Second, "the intervention presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical situation." This is an attempt at insuring that permission and assent are truly informed.

Third, the intervention can only represent a *minor* increase over minimal risk. The regulations don't specify what counts as a minor increase over minimal risk. Thus it is up to the IRB to decide whether interventions, such as placebo injections, sedation, and bronchoscopies are greater than a minor increase over minimal risk.

IRBs accept the challenge of interpreting the regulations. However, it has been twenty years since the Belmont Report and the problems with interpretation need more attention. While NBAC may be a good place to start, a more permanent forum would be useful to address the evolving conceptual challenges.

Procedural Issues. More important than the problems of conceptual vagueness, there are a number of procedural issues facing IRBs that pose greater risks to children, for which an improved centralized mechanism of oversight of research and IRBs is necessary.

The premise of the IRB approach is that local regulation, and in essence, self regulation, is adequate. While I believe that the IRB concept should be continued, there are significant modifications that should be made to keep up with the research landscape of the twenty first century:

1. A better mechanism for oversight and monitoring of multicenter trials is needed.
2. There needs to be more organized local oversight of community investigators practicing outside of academic institutions.
3. Research that falls outside of NIH or FDA purview should still be reviewed
4. There needs to a be a singular mechanism for oversight of IRBs.

Local review has the advantage of intimate knowledge of the investigators, their clinical practice, and their research experience, but the IRB may have conflicts of interests. If research is not approved, the institution may lose funding. This has become a greater problem with multicenter studies. Such studies are difficult to modify. When the IRBs have problems with the study design, they are often in the position of either accepting or rejecting the proposal. The concern is expressed that if the IRB rejects the proposal it will just be done somewhere else.

For example, the University of Arizona IRB has been asked to review a number of studies for anti-inflammatory treatments for childhood asthma. There are approved anti-inflammatory treatments for asthma including inhaled steroids. Often the study designs require treatment with investigational drugs or placebo. We have rejected some such studies because they deny an effective treatment. We hear from investigators that other IRBs have approved the study. Central oversight to allow modification of such protocols is worthwhile. As a consultant to the NIH for studies about genetic testing, I have had experience with central review of informed consent documents. I believe that there is a complementary role for centralized review.

An additional problem arises when such studies are conducted in the community settings. While the University of Arizona IRB did not permit the children in the asthma study to be taken off their medicines, the same study was done by a private clinician two miles up the road. The study was reviewed by an IRB in another state with which the investigator contracted and was approved.

There are several problems, in addition to even greater conflict of the direct payment for oversight. The review board is not from the same community. This diminishes the ability of the IRB to make judgments with direct knowledge of the behavior of the investigator. While IRBs approve consent *forms*, the consent *process* is left to the investigator. Even though the IRB knows what is presented in writing, it also needs some assurance that the investigator presents the study noncoercively. This is hard to do when the IRB does not have ongoing knowledge of the behavior and character of the investigator. Such an investigator may use different IRBs as well, preventing any single IRB from appreciating the research portfolio and practices of the investigator. In addition to variation in study design, different criteria for recruitment and reimbursement may be used. These are important issues when parents are making decisions that might put their children at risk.

The University of Arizona IRB requires that all advertisements exclude dollar amounts of reimbursement, to avoid attracting parents who were more interested in the money, *per se*. However, the non-university investigators publicize the reimbursement

figures. Also, the amount of reimbursement differs in this study, from approximately $250 to $750. Finally the University of Arizona IRB requires that payment be made in the form of a savings bond to the child, to clarify that this money was intended for the child, not the parent. Yet in the community setting there are even greater incentives for investigators to recruit patients as a direct source on income.

This is a problem that must be addressed as more research happens outside of academic institutions. In the community setting, the increased promotional activities, along with more risky studies, less review and the added financial benefit to the investigator, raises questions about the validity of "parental permission" and the ability to protect children from research risks. For these reasons, for profit IRBs provide less protection for children and I believe they should be prohibited. My recommendation is that, whenever feasible, all research be reviewed within the same community and that the same IRB should have jurisdiction over all of a particular investigator's protocols.

The problems of multicenter trials and community investigators point the need for greater oversight and coordination of IRB activities. The NIH and the FDA have mechanisms for oversight. But different IRBs may be reviewed by one or the other. Some research may even fall outside the review of either group. It would more appropriate to have a centralized agency that required all research to be reviewed and was responsible for the oversight of all IRBs.

Conclusions

There needs to be greater incentives to involve children in research that will allow safer application of clinical medicine. Conceptual issues regarding children that need further attention include definition of minimal risk, methods for evaluating the balance of risks and benefits, the use of placebos, and the role of assent in children and consent in adolescents. Procedural issues include improved ability to monitor variations in review of multicenter trials, community oversight of research, and uniform oversight of IRBs. Both the conceptual and procedural issues could be addressed by the establishment of a single agency that is responsible for oversight and coordination of research on humans conducted in the US. Addressing these issues will promote the well being of children by the advancement of research without exposing children to unnecessary harm.

Mr. SHAYS. I just don't quite understand. Literally, you could live in Florida and you could——

Dr. WILFOND. Absolutely.

Mr. SHAYS. Oh, yes? I didn't finish my question.

Mr. CAPLAN. No, he just meant you could live in Florida.

Dr. WILFOND. I'm sorry.

Mr. SHAYS. So absolutely means that if I made an application in St. Louis, I could?

Dr. WILFOND. Yes.

Mr. SHAYS. Or New York or Alaska or Hawaii?

Dr. WILFOND. Mm-hmm.

Dr. LURIE. Please don't send it to Alaska.

Mr. SHAYS. I hear you.

Dr. WILFOND. I think the problem is, we do face very challenging—in terms of the IRB in Arizona—with our own investigators, they're often very challenging decisions. Often we will have the investigators come before us and talk with us, try to hash things out, try to come to a compromise that seems to work. And we know who the investigators are. But when you mail to somewhere else in another State, it's not as easily done. The thing I also want to point out as an example of this is that these studies are being done around the country.

So it's not just a problem only out of the community IRB, but what ideally would be the best would be some way of there being some sort of additional centralized mechanism of review of these multicentered trials. Because what happened is, as of the study, the investigator came to us and said, look, if we don't do it they will do it somewhere else. Unfortunately, there was no way of us being able to communicate our concerns about the ethics of this study to someone else. It essentially was just up to us to say, it can't happen in Tucson. But there was nobody just who was looking out for everybody else.

Mr. CAPLAN. Just a quick comment on this point.

Mr. SHAYS. Sure. And then we'll get to you, Dr. Lurie.

Mr. CAPLAN. There are many situations, Mr. Chairman, in which local IRBs feel threatened by a private researcher saying, well, if you don't approve it, they will do it down the road, and we'll be down the road in no time. And that can cast a pall over a local IRB's willingness to get tough with a particular informed consent form or a particular protocol. Because it's well understood that there are other places to go for the private researcher.

Mr. SHAYS. Can I make an assumption that there are no conflicts on those who serve on those boards?

Mr. CAPLAN. Well, the conflict—you're right. You can't.

Mr. SHAYS. I cannot?

Mr. CAPLAN. You cannot make that assumption.

Mr. SHAYS. OK. We'll come back to this. You've whetted my appetite. Dr. Lurie.

Dr. LURIE. Good afternoon.

Mr. SHAYS. Good afternoon.

Dr. LURIE. I'm going to talk about three separate subjects today. I'm going to talk first about HIV vaccine trials. I'm going to second talk about the NIH-funded study in Anchorage, AK, on needle exchange. And then I'm going to talk as well about the African, Car-

ibbean, Thai mother to infant transmission studies that were discussed this morning.

Mr. SHAYS. Can you do that in 10 minutes?

Dr. LURIE. I would say so.

Mr. SHAYS. Yes. OK.

Dr. LURIE. There are several things that link these. One is the difficulty of obtaining informed consent in vulnerable populations. A second is the need to provide research subjects with state-of-the-art medical care. And the third is the conflict of interest between the purported needs of researchers about which we heard much this morning and the clear needs of research subjects about which we sometimes heard less.

Let me talk about the HIV vaccine trials first. We know that behavioral interventions such as safe sex counseling, the provision of condoms, the provision of sterile syringes have the ability to reduce the number of new HIV infections in any given group. And if you're setting up an HIV vaccine trial it therefore becomes ethically necessary to provide state-of-the-art counseling and other interventions to the subjects.

Now, the problem is that, to the extent that you are successful, there will be fewer HIV infections in your subjects. And that creates the "problem" over time of having more difficulty in establishing that, say, the vaccine is more effective than a placebo. This, I think, creates a real conflict of interest which I believe is best resolved with the following. Creating an independent group of people to provide counseling in these kinds of HIV vaccine trials separate from the investigators. Unfortunately, every time that this is raised as a proposal I always encounter resistance from people in Government and researchers. But I do think that that is a straight-forward answer to what is a real problem.

A second issue in HIV vaccine research involves the so-called gp120 HIV preventive vaccines. Now, back in June 1994 the AIDS Research Advisory Council, otherwise known as ARAC, found that the data were insufficient to support Government-funded studies in this country. But what we have now is a San Francisco based company named Vaxgen which is planning, with logistical and statistical help from the Centers for Disease Control and Prevention, to conduct an efficacy trial of gp120 in Thailand even though the vaccine has been rejected for efficacy trials by another arm of HHS—NIH—in this very country.

It seems unethical. It seems exploitative. Particularly because there really is no guarantee that Thai citizens will ultimately have access to any vaccine that's proven effective.

Subject 2, subject of the needle exchange program in Anchorage, AK. Since 1991, there have now been seven—count them—seven federally funded studies looking at whether or not needle exchange programs reduce the number of new HIV infections and whether they increase drug use or not, and every one of them has concluded that, yes, they reduce HIV infection, and no, they do not increase drug use. Despite that there is a plan to do a randomized control trial of needle exchange in Anchorage, AK. This despite that fact that the seventh of the studies that I mentioned was an NIH Consensus Development Panel which reached the same conclusion as its six predecessors.

Now we have NIH with a $2.8 million study in which people are going to be randomized either to needle exchange or else to a so-called enhanced pharmacy intervention, which means that if you try to get—they were going to give you information about how to walk, how to talk, how to dress when you go into a pharmacy and try to purchase syringes. Now, we see three problems with this study. Problem one, if you're not in the study you cannot go to the needle exchange. Problem two, if you're in the study, you only stand a 50–50 chance of going to the needle exchange. Now, that seems a problem seeing as though the researchers themselves admit in their protocol that this "represents the withholding of a potentially life saving service," the very thing that is precluded by the Nuremberg Code and practically every code thereafter.

The third problem with the study involves hepatitis B. And here the problem confronted by the researchers is that fortunately there is relatively little HIV in the drug users of Anchorage. And so they're using hepatitis B as a kind of a proxy marker because it's more common than HIV is. The problem is that there happens to be a very effective vaccine for hepatitis B, and so the researcher has a conflict of interest again, much like the situation with the behavioral intervention in the vaccine trials, whereby, to the extent that people are vaccinated, there will be fewer clinical outcomes and therefore it will be more difficult to show a difference between the two study groups.

Those are the problems that we raised in a series of letters to Dr. Varmus in the beginning of October 1996. And he immediately put the study on hold and convened a 10-person panel to review our concerns. The panel did not include anybody who was either a drug user or might be otherwise expected to represent their interests—like someone who runs a needle exchange. And it had a bunch of academics, many of whom were themselves recipients of grants from the National Institutes for Drug Abuse, in fact that very same division within the National Institutes of Drug Abuse and so, themselves, might have been reluctant to criticize the Institute.

That committee said, no, actually there's no problem with the study at all, it's fine. They signed off on the study completely. Fortunately, to his credit, Dr. Varmus went beyond what they had done and said, you need to do more to provide hepatitis B vaccine to people, although in our view he still didn't go far enough, because he should have required onsite vaccination of the subjects. And that didn't happen. To summarize, this unethical research proposal passed six levels of review. No. 1: the IRB at the University of Alaska. No. 2: the OPRR. No. 3——

Mr. SHAYS. Slow down. What was the second?

Dr. LURIE. The OPRR. The Office for Protection——

Mr. SHAYS. Yes. Right.

Dr. LURIE. Right. The third: the NIH AIDS Review Committee. The fourth: the panel that Dr. Varmus pulled together to review our complaint. The fifth: Advisory Committee to Dr. Varmus. And then finally: Dr. Varmus himself. Yet, despite this—and as Dr. Caplan quite accurately pointed out—the meat and potatoes of Ethics Review Committee work is looking at informed consent forms. There was no mention of any inadequacies in the informed consent

form, despite the fact that the informed consent form failed to include such basic information as that the researcher believed—again, in their own words—that this was a potentially life saving service, that the researchers estimate that the drug users in the pharmacy group were at up to four times increased risk of getting hepatitis B.

And importantly it didn't explain that if you were a drug user assigned to the pharmacy and you showed up at the needle exchange, they'd ask you for your card, if your card showed that you were, in fact, somebody assigned to the pharmacy group, they'd send you packing with more information about how to walk and talk and a buildings map for Alaska so that you could find the pharmacies. And finally, it didn't make any mention whatsoever of hepatitis B vaccine.

The informed consent form had other problems. A readability analysis was done—and, again, this was alluded to earlier—and the degree of schooling that was needed for this was 15 years of schooling to be able to read the informed consent form, this despite the fact that Dr. Fisher, who had done readability analyses with the drug users of Anchorage had himself concluded that the drug users of Anchorage read with a ninth grade level. And the informed consent form, which all six of these reviews said was OK, finally, because of the attention that we drew to it, was reviewed and reviewed and reviewed and revised and revised and revised over and over again until instead of being two pages long, it is five pages long.

Even so, it still contains a new fiction which had not been in the previous ones, which is that there is no other needle exchange program in Anchorage. And that is incorrect. Back in December 1996, a new needle exchange did open. And this was trumpeted on the front page of the Anchorage Daily News. The investigator acknowledged it in a national magazine. And it was on Anchorage television station as well. So this is a well known, blatant falsehood right there in the informed consent form.

Mr. SHAYS. Let me do this. We have 15 minutes. I'd like Ms. Flynn to kind of get some on the record before we break. So if you want to——

Dr. LURIE. I just want to talk about the Africa stuff——

Ms. FLYNN. It's all right.

Mr. SHAYS. OK. I think what I want to do, Ms. Flynn, is have you go, and then we'll come back to you.

Dr. LURIE. OK.

Mr. SHAYS. We'll be able to get that on the record.

[The prepared statement of Dr. Lurie follows:]

Thank you for the opportunity to testify before the Subcommittee on these crucial bioethical issues. Our testimony today will address two subjects: HIV vaccine trials and a National Institutes of Health (NIH)-funded study of needle exchange programs in Alaska. While these two areas may seem disparate, there are several common themes that link them: 1. the difficulty of obtaining informed consent in vulnerable populations; 2. the need to provide research subjects with state-of-the-art medical care; and 3. the conflict of interest between the purported needs of researchers and the clear needs of the research subjects. We will address HIV vaccine trials first.

There is no question that the development and widespread utilization of a vaccine that effectively prevents transmission of HIV would be a public health triumph. With behavioral interventions currently having an important but limited impact upon HIV transmission, an effective vaccine is our best hope for preventing the huge burden of suffering from HIV disease both in the U.S. and abroad. Yet enormous ethical issues complicate potential vaccine efficacy trials. We shall mention just three.

First, because behavioral interventions such as safe sex counseling or the provision of condoms or sterile syringes have the capacity to reduce HIV risk behavior, it is critical to provide research subjects with state-of-the-art behavioral interventions as part of HIV vaccine trials. Yet, to the extent that such interventions are effective, there will be fewer new HIV infections and the ability to demonstrate statistically significant reductions in new HIV infections due to the vaccine will be reduced. This places the researcher in a classic conflict of interest, and creates an incentive to not provide adequate behavioral interventions in conjunction with these vaccine trials. The obvious solution to this dilemma is to employ an independent group of individuals to provide the behavioral interventions, but on several occasions when this has been suggested in the context of HIV vaccine trials it has met with opposition.

The remaining two issues deal with potential HIV vaccine trials in developing countries. Worldwide, an estimated 21.8 million people are presently living with HIV. Over 94% of these individuals live in the developing world; residents of developing countries therefore stand to derive the greatest benefit from such a vaccine. The need for a *vaccine* for a particular country is, however, different from the need for a *vaccine trial* in that country.

The Council for International Organizations of Medical Sciences' ethical guidelines on research in developing countries state unequivocally that "the

ethical standards applied should be no less exacting than they would be in the case of research carried out in [the sponsoring] country." Yet there are already worrisome signs that this fundamental ethical precept will be ignored.

In June 1994, research on two so-called gp120 HIV preventive vaccines was reviewed by the blue-ribbon AIDS Research Advisory Committee (ARAC) of the NIH, and the data were found to be insufficient to support government-funded efficacy trials in the U.S. As far as we know, no data have since been generated that would alter that assessment; indeed reports of a dozen breakthrough infections among subjects fully vaccinated with gp120 have raised further doubts about these vaccines' efficacy. Since 1994, most attention in the HIV vaccine field has now shifted to the so-called ALVAC-HIV vaccine. Yet San Francisco-based Vaxgen is planning, with logistical and statistical help from the Centers for Disease Control and Prevention, to conduct a Phase III trial of its gp120 vaccine in Thailand, even though that vaccine had been rejected for efficacy trials in this country. This seems unethical and exploitative, particularly as there is no guarantee that Thai citizens or those of other developing countries will have access to the vaccine should it be proved effective. Is Vaxgen planning on disclosing to Thai subjects that the vaccine was rejected by U.S. scientists for tests in our country?

Finally, some subjects in vaccine trials will contract HIV infections, either because they are randomized to the placebo group or because the vaccine is not completely effective (or perhaps not effective at all). While such newly infected individuals in industrialized country trials can be referred for care, there is concern that, in the developing countries where HIV vaccine trials are being considered, effective anti-HIV drugs will not be provided to those who become infected during the trial. We believe that it is the researchers' ethical responsibility to ensure that antiviral drugs are provided to all individuals who develop HIV infection during the trial, particularly because participation in such trials may lead some subjects to believe that they are protected from HIV infection and may thus induce them to increase their risk behavior.

We will now turn to the subject of research on needle exchange programs, which again illustrates the need for particular vigilance when conducting research on vulnerable populations.

Since 1991, there have been seven federally funded reviews of the effectiveness of needle exchange programs in preventing the transmission of HIV infection between injection drug users and from the drug users to their

sex partners and children. Every one of those reviews has concluded that needle exchange programs reduce the transmission of HIV infection and that there is no evidence that they lead to increases in community levels of drug use. Even Health and Human Services Secretary Donna Shalala finally conceded in February 1997 that needle exchange programs reduce the number of new HIV infections, although she still failed to remove the ban on federal funding for needle exchange programs.

Despite this unanimity in the research world, including a recent NIH Consensus Development Panel, the NIH has decided to provide $2.8 million for a randomized, controlled trial of the effectiveness of needle exchange to be conducted by Dr. Dennis Fisher of the University of Alaska Anchorage. It is worth noting that, although there is no evidence from a randomized controlled trial that condoms reduce the number of new HIV infections, no-one would consider such a study and effective public health policy has been formulated even in the absence of such evidence.

At least 600 injection drug users will be randomized to either receive sterile syringes for free from a needle exchange program or to receiving information on how to purchase syringes from pharmacies in Anchorage, information all or most will already have. When a subject seeks to obtain syringes at the needle exchange program, the researchers will use the subject's bar-coded identification card to generate the subject's image on a computer screen and thereby establish to which arm of the study the subject has been randomized; those assigned to the pharmacy condition will be turned away and advised how to purchase syringes at pharmacies. Remarkably, the researchers themselves admit in their grant proposal that this "represents the withholding of a potentially life-saving service." Because HIV infection is relatively rare among the drug injectors of Anchorage, the researchers plan to measure the number of new infections with hepatitis B. This will act as a proxy for HIV infection and will allow the researchers to compare the effectiveness of the needle exchange and pharmacy groups in reducing blood-borne infection.

The research is unethical for at least three reasons:

1. If an injection drug user does not enroll in the study, he or she cannot use the needle exchange program at all, thus coercing subjects to enroll;

2. Of injection drug users who enroll in the study, only 50% will be permitted to attend the needle exchange program; the others will be turned away if they seek syringes at the needle exchange program; and

3. The research protocol does not provide adequate assurance that the subjects will receive hepatitis B vaccine. It is highly inappropriate to monitor injecting drug users in both research groups contracting potentially fatal hepatitis B infection when an extremely effective vaccine for hepatitis B exists. It is difficult to imagine an analogous study in which babies were monitored for the occurrence of tetanus, while not being provided with the existing vaccine. But the researchers are faced with a conflict of interest analogous to that regarding behavioral counseling in HIV vaccine trials: if compliance with vaccination is high, there will not be enough new hepatitis B infections to permit statistically meaningful conclusions.

The parallels between the Alaska study and the notorious Tuskegee syphilis study are clear. In Tuskegee, poor rural African American men were denied access to proven treatment for syphilis and went on to develop the disease's complications, including death. In the Alaska study, another group of vulnerable Americans, injection drug users, many of whom are Native American or African American, are being placed at risk for life-threatening infections by being denied adequate access to not one, but two, proven medical interventions: sterile syringes and hepatitis B vaccine.

Indeed, there is an ugly racial dimension to the issue of sterile syringe availability in Anchorage. When we sent casually dressed volunteers to survey pharmacies in Anchorage, only 14% of pharmacies were willing to sell syringes without encumbrance. But an African American woman volunteer was refused syringes at all five pharmacies she visited, including two that had sold syringes to non-African Americans the day before.

When Public Citizen's Health Research Group raised these issues in a series of letters to NIH Director Harold Varmus beginning in October 1996, he immediately put the study on hold and convened a ten-person panel to review our concerns. The panel did not include anyone who could represent the concerns of drug users (such as injection drug users themselves or people who operate needle exchange programs) and instead was comprised primarily of academics, many of whom have obtained research funding from the National Institute of Drug Abuse and may have been reluctant to criticize the Institute. It was no great surprise, therefore, when the panel found no problems with the study design and recommended that it proceed as approved. To his credit, Dr. Varmus went beyond the blanket endorsement of the panel to require expanded efforts to provide hepatitis B vaccine, but still fell short of offering on-site vaccination, which would be the best way of increasing compliance with the three-injection vaccination regimen. Counseling patients about the hepatitis B vaccine and then sending them elsewhere to receive it not only introduces a delay in receiving the vaccine,

but also conveys the impression that the investigators believe that receiving the vaccine is not urgent.

Astonishingly, this blatantly unethical research proposal passed review at multiple levels:

1. The Institutional Review Board at the University of Alaska Anchorage;
2. The NIH's Office for Protection from Research Risks;
3. The National Institute on Drug Abuse's AIDS Review Committee;
4. The panel convened by Dr. Varmus to review the study;
5. The Advisory Committee to the Director of NIH; and
6. Dr. Varmus himself.

The inadequacy of local Institutional Review Board review merits special mention. As a recent General Accounting Office report concluded, some Boards devote only one to two minutes to each study they review and their independence is hampered by "close collegial ties with researchers at their institution." The Cleveland Plain Dealer recently disclosed that of 942 Food and Drug Administration inspections of Institutional Review Boards between 1990 and 1996, 40% revealed poor or missing voting records, 19% showed missing informed consent forms, injury reports or research protocols, and 16% demonstrated that subjects had not been clearly told that the procedures in the study were experimental. In a shocking 13% of inspections, subjects were not offered proven alternative treatments, similar to the situation here.

At no point in these reviews was the adequacy of informed consent called into question, despite an original informed consent form which failed to disclose the following essential pieces of information:

1. The researchers believe that needle exchange is, in their own words, "a potentially life-saving service";
2. The researchers estimate that injection drug users in the pharmacy group are at up to four times increased risk for hepatitis B compared to the needle exchange group;
3. Drug users who don't sign up for the study cannot attend the needle exchange program;
4. Drug users assigned to the pharmacy condition cannot attend the needle exchange program;
5. Drug users assigned to the pharmacy condition who attempt to obtain syringes at the needle exchange program will be turned away;
6. The syringes at the needle exchange program are free;

7. The needle exchange program, unlike the pharmacy, will provide other free services such as condoms, bleach, alcohol wipes, sterile water and HIV prevention literature;
8. The researchers will be monitoring drug users to see if they develop sometimes fatal hepatitis B infection, even though there is a vaccine that could prevent it; and
9. According to the federal government, providing this vaccine to all susceptible drug injectors is the standard of care.

In addition, a readability analysis of the original informed consent form shows that it required a reading level equivalent to 15 years of schooling, even though Dr. Fisher's own research demonstrates that Anchorage injection drug users read at a 9th grade level. As a result of the enhanced scrutiny this grant has generated, the informed consent form has now been modified from its original two to the present five pages and some, although not all, of our objections have been addressed. But the researchers have introduced, and the University of Alaska Institutional Review Board and the NIH have accepted, a new fiction into the informed consent form: that there is no other needle exchange program in Anchorage. Actually, in an effort to reduce the harm from the Alaska experiment, volunteers in Anchorage have set up a needle exchange open to all injection drug users, a fact that was noted by Dr. Fisher himself in a national magazine and which received front page coverage in the Anchorage Daily News on December 23, 1996 and was featured on an Anchorage television station.

As important as informed consent is in this situation, there is one overriding point: not even a perfect informed consent form can make ethical a study that is unethical in design, particularly one that needlessly puts subjects at risk for fatal infectious diseases. The only ethical solution to the situation in Alaska is to cut off funding for the study until it is redesigned so that all drug injectors have access to the needle exchange program and intensive efforts are made to provide hepatitis B vaccination to all drug users in the study.

Ms. FLYNN. All right. Thank you. Thank you, Chairman Shays. I appreciate very much the opportunity to appear before the subcommittee today. I am a member of the President's National Bioethics Advisory Council. Within my day-to-day work for the past 12½ years, I've served as executive director of the National Alliance for the Mentally Ill, which is a large, grass roots, family and consumer organization concerned with issues that affect the lives of people with severe mental illnesses, including schizophrenia, bipolar disorder, major depression and other disabling mental illnesses.

We are families. We are patients. We are the grass roots. We are the folks who rely on the kinds of protections of human subjects that have been addressed repeatedly today. From the beginning of our organization we have been very strong supporter and advocates for biomedical research on severe mental illnesses. Such research has yielded remarkable breakthroughs in the understanding and treatment of these disorders, which are among the most devastating known to mankind.

We particularly look to the development of promising new medications for the treatment of schizophrenia and other debilitating brain disorders, which have occurred as a direct result of biomedical research. We've also had great advances in understanding the ideology of brain disorders, advances that we believe may ultimately lead to much better control of symptoms and even potentially cures. And it's important, as has been noted several times today that none of these advances that have been so dramatic in treatment of mental disorders would have been possible without the participation of individuals who suffer from these disorders.

And I think it's important to note that they are not just subjects but indeed participants in the research, which I think is a stronger term and a more appropriate term. And at least in the view of NAMI members, they are really the heroes here in the research arena. It is, however, very important, as we confront these issues, to try to strike the balance so that we can maintain a healthy climate for research, which all of us view as the long-term hope for conquering these illnesses.

And so it's important that we look at the issues that surround many of the complex ethical questions that you have raised with this hearing. The use of human subjects in research presumes that individuals who participate are capable of comprehending the nature and scope of the research and, therefore, can participate in an informed way and consent to their participation. But as you know, the nature of severe mental illnesses often renders individuals with these disorders sometimes incapable of such consent. It is good to see the dialog we've had today. And it is good to note that scientists join bioethicists and advocates in being committed to balancing the importance of creating and maintaining a healthy climate for vital research with the equally important paramount concern of protecting vulnerable subjects who may lack the capacity to fully understand the nature, the risks and the benefits of the research they're asked to participate in.

Recently, there have been a number of issues which have received a great deal of attention, including revelation several years ago about specific research protocols at UCLA Neuropsychiatric Re-

search Institute, in which it has been alleged and, indeed confirmed, that there were flaws in the informed consent procedures. And there continue to be concerns about whether this research was conducted in the highest possible ethical manner. Members of NAMI obviously looked at this situation with great concern.

And for the past several years we have brought our concerns about this study to the officials at the National Institute of Mental Health and the Office for Protection from Research Risks. The entire lay board of the National Alliance, after hearing from a great many experts, consultants, family members moved forward in February 1995 to adopt some very straightforward and, we think, very helpful concrete suggestions as policies that I would like to share with you at this hearing.

Mr. SHAYS. Can you say the last statement you made? I got distracted. What was the last point?

Ms. FLYNN. That in February 1995 the lay board of the National Alliance, again, made up of families and patients, adopted some specific policies that I would like to share with the subcommittee today, which we think will offer some of the concrete guidance that you are looking for and ways to strengthen the climate that we currently have. I guess I'm not certain, sir, whether you want me to try to deliver my entire——

Mr. SHAYS. No. You have about 3 or 4 more minutes, if you'd like to continue.

Ms. FLYNN. OK. Well, let me try to move forward, then, and just try to capsulize. Because my written statement does go into greater detail. Let me just try to move forward and try to highlight what the specific policies are that we think need to be adopted.

Mr. SHAYS. And we'll be able to cover some of it in the questioning part as well.

Ms. FLYNN. OK. Thank you.

Mr. TOWNS. The entire statement will be included in the record.

Mr. SHAYS. Yes.

Ms. FLYNN. I appreciate that. We would like to see national standards developed to govern voluntary consent, comprehensive exchange of information and related protections of persons with cognitive impairments who become research subjects, and that the development of these national standards must include individuals who have these disorders, their family care givers, who are directly involved and directly affected. We note that there is not currently existing in Federal regulations specific protections for this vulnerable population, although they have been highlighted by several prior national ethical bodies as needing this kind of support.

We believe that the National Institute of Mental Health, which funds the great bulk of research on severe mental illnesses, should take the lead in the development of such national standards. And we are pleased to see that Dr. Steven Hyman, the new NIMH director has moved forward to convene a group that will be looking at the development of not only standards, but potentially best practices and other guidance to the research community to strengthen the way in which informed consent and other psychiatric issues in research are handled.

We think it's important to note that informed consent as has been referenced is not just the gaining of a signature at the front

end of a research protocol. But particularly for vulnerable subjects who may be cognitively impaired, it needs to be seen as an ongoing process. Comprehensive information needs to be provided both orally and in writing, including information that makes clear not only the risks and benefits of research, the scope, scale and objectives of the research, but also other modes of treatment, other options than the research that may be available.

This is important because of unique characteristics of most people in this country with serious mental illness, Mr. Chairman, who frequently do not have health care coverage except through the public mental health system. These folks are uniquely vulnerable to the potentially coercive effects of being able to access novel or experimental or potentially more valuable treatment through research settings.

We believe that it is very, very important that the capacity of individuals to participate in research be assessed not only at the outset, should there be any question, but also be able to be assessed continuously through the research should there be any question of their continuing ability to consent, and that that should be conducted by someone not directly involved in the research, as I think has been noted previously. Should it be determined that the individual lacks decisional capacity, surrogate consent should be sought from family members, if they are willing and able. And here we are particularly concerned that family members are often not involved, not informed, and not able to then participate on behalf of a relative that may have fluctuating ability to consent and participate.

Institutional review boards which review research on mental illness must include consumers and family members with direct personal experience with these severe and debilitating illnesses. It has been our experience that most IRBs do not get this kind of representation from the community, even when they do a regular review of psychiatric research protocols. This is something that can be addressed easily. This is something that our organization is in a position to be a resource on. And we think there should be strong guidance to IRBs, that they should include representatives of the community of individuals with psychiatric illness.

We believe that investigators must ensure that individuals who participate in research as outpatients, where most of this research, including research on new medications is conducted, they need to be linked to appropriate care, treatment and supports for the entire duration of the research.

Mr. SHAYS. I need you to finish up here because we have two votes.

Ms. FLYNN. All right. One final point, then. Let me say that many people enter into research on new medications because they hope for great improvement in their treatment. We then find that when the research is over—9 weeks, 12 weeks—that the medication is no longer available to them. We find this unethical. We find this a procedure that truly can be very damaging. And we believe that when there are protocols approved that involved offering new

medications to individuals who may have no other way to get them, that they must be guaranteed that they will be able to continue if the medication has been seen as safe and effective even beyond their tenure in the research program.

[The prepared statement of Ms. Flynn follows:]

Chairman Shays, Congressman Towns and Members of the Subcommittee, my name is Laurie M. Flynn and I am the Executive Director of the National Alliance for the Mentally Ill (NAMI). I very much appreciate the opportunity to appear before this Subcommittee today. In addition to my role as NAMI's Executive Director, I am a member of President Clinton's National Bioethics Advisory Council (NBAC).

NAMI is the nation's largest grassroots organization dedicated to improving the lives of persons with severe mental illnesses, including schizophrenia, bipolar disorder (manic-depressive illness), major depression, obsessive-compulsive disorder, and anxiety disorders. NAMI's membership includes more than 140,000 people with severe mental illnesses and their families, and 1,100 state and local affiliates in all 50 states, the District of Columbia, Puerto Rico and Canada. NAMI's mission includes advocacy for nondiscriminatory and effective federal and state policies, research into the causes, symptoms and treatments for severe mental illnesses and education to eliminate the pervasive stigma toward those who suffer from these serious brain disorders.

NAMI has been and will continue to be a strong advocate for biomedical research on severe mental illnesses. Biomedical research has yielded remarkable breakthroughs in the understanding and treatment of severe mental illnesses. The development of promising new medications for the treatment of schizophrenia and other debilitating brain disorders have occurred as a result of biomedical research. So too have advances in understanding the causes and etiology of these brain disorders, advances which may ultimately result in the ability to control and even cure the symptoms of these illnesses. These remarkable advances would not have occurred without the participation of individuals with severe mental illnesses as human subjects in research. These individuals, many of whom are NAMI members, are heroes in the struggle to overcome these devastating brain disorders.

Because of these remarkable advances, it is critically important to maintain a climate conducive to biomedical research on severe mental illnesses. It is equally important to address the complex ethical questions concerning the use of human subjects in research of this nature. The use of human subjects in biomedical research presumes that individuals who participate are capable of comprehending the nature and scope of the research and can therefore consent on an informed basis to such participation. However, the nature of

severe mental illnesses render individuals who suffer from these disorders sometimes incapable of providing such consent. I believe that scientists, bioethicists, and advocates are committed to balancing the importance of maintaining a healthy climate for research with protecting vulnerable subjects who may lack capacity to fully understand the nature, risks and benefits of the research they are participating in. We welcome this dialogue as vital to fostering our partnership with science.

Recently, these issues have received renewed attention since revelations, a few years ago, that a specific psychiatric research protocol at the UCLA Neuropsychiatric Research Institute (one of the nation's largest psychiatric research programs) may not have included adequate informed consent and other procedures for fully informing research participants or their families about the potential risks and benefits of this protocol. We have discussed our concerns about this study with officials at the National Institute of Mental Health (NIMH) and the Office for Protection from Research Risks (OPRR). In February 1995, in response to the concerns engendered by the UCLA case, the NAMI Board of Directors, after extensive consultation with outside experts, adopted comprehensive policies addressing protections of individuals who participate as human subjects in research. (These policies are attached to this testimony as Appendix I).

Since adoption of these policies, I have worked actively within the psychiatric research community to promote adoption of practices reflecting the principles embedded in these policies. While the time allotted to me will not allow me to present all of these policy recommendations at this hearing, I would like to use this opportunity to submit those which I believe to be most important to this Subcommittee for its consideration.

First, it is important to distinguish between research and treatment for persons with severe mental illnesses. Due to the inadequacies of many treatment systems and pervasive discrimination in health insurance coverage of severe mental illnesses, many individuals with schizophrenia, manic-depressive illness and other serious brain disorders do not have access to treatments which could benefit them. Most of these individuals are reliant on underfunded public mental health systems for their care and treatment. Most are Medicaid recipients, due to their extreme poverty and disability. Because of the failures of public mental health systems, many individuals with severe mental illnesses must turn to research protocols for access to

promising new medications. Consequently, the boundary lines between clinical treatment and research have been somewhat blurred.

Nevertheless, there are significant distinctions between clinical treatment and research. While clinical treatment programs are designed solely to benefit individuals who participate in them, this is frequently not the case with research. Some research protocols are designed to produce basic information about characteristics or patterns of specific brain disorders, with no expectation that the research will yield specific benefits for individuals who participate in these protocols. Other protocols are designed to assess the progression and course of specific disorders, without focus on treatments to alleviate the symptoms of these disorders. For example, the UCLA study in question involved a relapse protocol: research subjects were withdrawn from their medications specifically to study relapse patterns.

Even research protocols which are designed to study potentially beneficial treatments of severe mental illnesses may not prove beneficial to individual participants. Many new medication protocols are designed as placebo controlled studies, i.e. some participants are administered the medication being studied and some are administered placebo. In studies of this nature, there is no guarantee that individual participants will ever be administered the new medication under study.

Finally, biomedical research on the causes and treatments of severe mental illnesses involve varying degrees of risk for individual participants. Some protocols involve minimal risks to individual participants, e.g. studies which involve no more than a blood test, whereas other protocols involve risks which are potentially quite significant, e.g. early trials of new medications with unknown potential benefits or side effects.

These multiple factors, i.e. the cognitive impairments of individuals who participate as human subjects in psychiatric research, the unknown clinical benefits of such research, and the potential risks of research together mitigate strongly in favor of the need for comprehensive, strengthened procedures for protecting the best interests of these vulnerable individuals. The remainder of my presentation will focus on certain steps which can be taken, in accordance with NAMI's policies, to improve these protections.

(1) National standards to govern voluntary consent, comprehensive exchange of information, and related protections of persons with

cognitive impairments who become research subjects must be developed and they must include the interests of persons who become human subjects, families, and other caregivers.

Two national Commissions - The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979) and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1981) identified persons with mental illnesses as a particularly vulnerable group and therefore recommended special protections for these individuals in future Federal regulations governing biomedical research.[i] Despite this, the Federal Regulations which were adopted did not include persons with severe mental illnesses among the vulnerable populations listed as needing special protections. These regulations set forth specific elements required for the provision of informed consent for all research involving greater than minimal risks for individual subjects.[ii] However, these regulations are silent concerning special factors which must be considered concerning the provision of information about specific research and the process of obtaining fully informed consent from individuals who have cognitive impairments.

For example, the capacity of an individual with a cognitive impairment may fluctuate over periods of time. While an individual may be capable of comprehending the nature of a specific research protocol at the beginning of the process (the time when informed consent is typically provided), his/her capacity to comprehend may be impaired at some point during the research process. Nevertheless, the regulations do not address the importance of the ongoing provision of information to the research subject throughout the research process (which, in the case of some protocols, may be rather lengthy).

Similarly, the regulations do not address the importance of providing information to family members or others who function as caregivers in the lives of persons with cognitive impairments. There is a presumption implicit in the regulations that if an individual does not have a legal guardian or representative, there is no obligation to communicate information about the research to anyone other than the individual, including members of his/her family. Finally, the regulations do not provide guidance concerning surrogate consent and other procedures which should be utilized when individuals are determined to lack capacity to provide informed consent.

Scientists involved in research on Alzheimer's Disease and other neurological disorders impacting primarily on senior citizens have done important work in developing mechanisms for (a) considering when surrogate consent may be appropriate in biomedical research, and (b) determining who may appropriately provide surrogate consent in specific types of biomedical research. These guidelines have been incorporated, in part, into draft legislation in Maryland addressing informed consent and other protections for decisionally incapacitated subjects in research. They may serve as a valuable tool for scientists, bioethicists, and advocates concerned about developing similar procedures governing research on persons with severe mental illnesses.

The lack of guidance specific to research on subjects with cognitive impairments speaks to the need to develop general, national standards governing research of this nature. Since the National Institute of Mental Health (NIMH) funds more than 75% of all biomedical research on severe mental illness, NAMI believes that it should take the lead, in concert with other federal agencies funding research conducted on individuals with cognitive impairments, to promulgate such standards. Persons with severe mental illnesses, family members, and other stakeholders should be integrally involved in this process. NAMI is pleased that NIMH Director Steven Hyman, M.D., has begun such a process.

The development of national standards governing research on individuals with cognitive impairments must emphasize that informed consent is an ongoing process and that individual research subjects should be provided with comprehensive information, orally and in writing, throughout the research process. This should include information about the purposes and scale of the research, the objectives of the research, the likely research process, the potential benefits and risks of the research, and treatment options available to the research subject, in lieu of research. Specific information should also be provided about the role and functions of the Institutional Review Board (IRB) and who to contact in the event that the research subject or his/her family have questions or concerns about the research. NAMI believes that the development of model policies and practices would be extremely useful to IRBs and the research community.

(2) Research participants should be carefully evaluated before and throughout the research for their capacity to comprehend information and their capacity to consent to continued participation in the research.

The determination of competence shall be made by someone other than the principal investigator or others involved in the research. Except for research protocols approved by the Institutional Review Board (IRB) as minimal risk, whenever it is determined that the subject is not able to continue to provide consent, consent to continued participation shall be sought from families or others legally entrusted to act in the participant's best interests.

There are three important principals embedded in this policy. First, since persons suffering from severe mental illnesses such as schizophrenia frequently experience fluctuations in decisional capacity, the capacity of all individuals with these disorders who participate as human subjects in research should be monitored on an ongoing basis. Research on those persons most impaired by severe mental illnesses is critical, as these brain disorders are often devastating. But research of this type must be conducted with special attention to the cognitive impairments which characterize these diseases.

Second, if questions arise concerning an individual's capacity to provide initial or ongoing informed consent, an immediate, thorough assessment of capacity should occur. Since the ability of the principal investigator or his/her staff to conduct objective assessments may be compromised, the assessment should be conducted by a qualified individual who is not directly involved in the research.

Finally, if it is determined that an individual lacks decisional capacity, substitute consent should be sought. Unless there are indications to the contrary, family members should be asked to provide substitute consent. If no family members are willing or able to function in this capacity, substitute consent should be permitted only from one who has been legally entrusted to function in this capacity, e.g. an individual assigned durable power of attorney pursuant to a properly executed advance directive or an alternative legal mechanism for assigning a proxy.

(3) Institutional Review Boards that regularly review research proposals for severe mental illnesses must include consumers and family members who have direct and personal experience with these brain disorders.

At many universities and research facilities, one Institutional Review Board (IRB) has responsibility for reviewing and approving all research conducted at these facilities. There are no assurances that anyone serving on these IRBs has specific knowledge about severe mental illnesses or research conducted on these illnesses.

NAMI strongly believes that all IRBs approving research on severe mental illnesses must include (a) at least one person, and preferably more, with knowledge of severe mental illnesses, and (b) a person with a severe mental illness or a family member of someone with an illness. If this is not possible, then IRBs considering research protocols on severe mental illnesses should be required to consult with individuals who have direct experience with these illnesses before approving a specific protocol.

Additionally, IRBs approving research on individuals with severe mental illnesses must receive specialized training about these disorders and issues pertinent to the participation of individuals with these disorders in research protocols. Persons with severe mental illnesses and their families should be involved in designing and conducting this training.

(4) Investigators must ensure that individuals who participate in research as outpatients are linked to appropriate care, treatment and supports for the entire duration of the research protocol.

Today, most biomedical research on severe mental illnesses is conducted on an outpatient basis. Individuals with these illnesses who participate in research may be particularly vulnerable to relapse or decompensation due to exacerbation of their psychiatric symptoms. This is especially, but not uniquely true, when the protocol involves "drug washouts" (i.e. withdrawal from psychotropic medications).

The potential implications of relapse or decompensation can be devastating for individuals with severe mental illnesses and their families. These consequences can include broken relationships, loss of housing and supports, homelessness, petty crimes, victimization, violence, or arrest and incarceration. Consequently, researchers have an important ethical and moral obligation to ensure that all vulnerable research participants are linked to treatment which can be accessed on a timely basis for as long as needed. Since families are generally the first to recognize signs of relapse,

investigators and their staff must also be prepared to respond to family questions and concerns on a timely and appropriate basis.

5. All participants in research protocols involving the assessment of new medications must be provided with opportunities by the investigator for a trial on the medication being studied, so long as other research on the new medication has demonstrated potential safety and efficacy.

Many research protocols evaluating the efficacy and safety of experimental medications for the treatment of severe mental illnesses are designed as placebo controlled studies. These studies typically include one group of subjects who receive the experimental treatment and one group of subjects who are administered placebo. In these studies, researchers are precluded from informing subjects of the group they are in. Consequently, individuals in critical need of treatment may think that they are receiving an experimental treatment, when in fact they are being administered a placebo.

NAMI has serious questions about whether placebo controlled studies are still necessary in this era. We believe that it is important to address whether standard therapies can be used as the comparison drug. We believe that the Food and Drug Administration (FDA), the National Institute of Mental Health (NIMH) and other involved federal agencies be urged to evaluate the need for this approach and to report back to the Subcommittee on a timely basis.

Additionally, NAMI strongly believes that all individuals participating in protocols involving the evaluation of experimental medications should be afforded the opportunity for a trial on the experimental treatment. Therefore, if individuals receive placebo as part of the study design, they should receive a trial on the new medication following completion of the placebo phase.

(6) All individuals who have benefited from the administration of experimental medications in research should be provided with continual access to the medication by the investigator without cost until a source of third-party payment is found.

Recently, I received a call from an old friend who suffers from schizophrenia. She informed me that after two successful years on an

experimental medication for schizophrenia, she had been taken off the medication because the drug company funding the research would no longer pay for her to receive the medication. Consequently, she is now desperately searching for a new protocol which she can participate in to receive the medication until it is approved by the FDA.

Unfortunately, sad stories like these are all too common for persons with severe mental illnesses. While drug companies frequently try to make experimental medications available free of charge to people who have successfully completed trials for fixed periods of time, the time limits established by these companies, coupled with the lengthy drug approval process, result in many people suffering relapses after being terminated from these drugs for lack of funding.

In view of the sacrifices made by people who voluntarily participate in trials of experimental medications, NAMI believes that all individuals should have continuing access to medications they have benefited from until alternative sources of funding are found. This, we believe, would be reasonable compensation for the contributions made by individuals who participate as human subjects in research.

Conclusion

NAMI supports the critical need for biomedical research on severe mental illnesses. I know first hand the benefits of such research. My daughter and other family members have participated in and benefited from NIMH funded research on new medications. NAMI is eager to play a role in strengthening protections of human subjects and ensuring ongoing improvements in research on severe mental illnesses through open dialogue with the scientific community. As the ultimate beneficiaries of research on brain disorders, NAMI members appreciate the interests of this Committee on these important issues.

The complete NAMI policies are attached as an appendix to our written testimony. I look forward to any questions you may have.

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[i] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, "The Belmont Report", April 18, 1979; President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, "Protecting Human Subjects", Dec. 1981.

[ii] 45 C.F.R. 46.116

Policies on strengthened standards for protection of individuals with severe mental illnesses who participate as human subjects in research.
(Adopted by the NAMI Board of Directors, 2/4/95)

1. **NAMI accepts the critical necessity for research using human subjects, acknowledges the important contribution of persons who become human subjects, and affirms that all such research should be conducted in accordance with the highest medical, ethical and scientific standards.**

2. **National standards to govern voluntary consent, comprehensive exchange of information, and related protections of persons with cognitive impairments who become research subjects must be developed, in which the interests of persons who become human subjects, families and other caregivers are included.**

3(A). **Participants in research and their involved family members must be fully and continuously informed, orally and in writing, about all aspects of the research throughout the process. Research investigators must provide information in a clear, accessible manner to ensure that participants and their involved families fully understand the nature, risks and benefits of the research.**

3(B). **The consent protocol must provide information which is clear and understandable on an individual basis for each participant and their family members. The consent protocol must provide information on the purposes and scale of the research, what is hoped to be learned and prospects for success, potential benefits and potential risks to the individual (including options for treatment other than participation in research, since research is not the same as treatment). The consent protocol should also contain information concerning the function of the Institutional Review Board (IRB), the identity of the IRB Administrator, the address and telephone number of the IRB administrator and other information, as appropriate.**

3(C). Whenever consent is given by someone other than the research participant, the participant and involved family members must receive information on the same basis as the person actually giving consent.

4. Research participants should be carefully evaluated before and throughout the research for their capacity to comprehend information and their capacity to consent to continued participation in the research. The determination of competence shall be made by someone other than the principal investigator or others involved in the research. Except for research protocols approved by the Institutional Review Board (IRB) as minimal risk, whenever it is determined that the subject is not able to continue to provide consent, consent to continue participation in the research shall be sought from families or others legally entrusted to act in the participant's best interests.

5. Institutional Review Boards which regularly review research proposals on severe mental illnesses must include consumers and family members who have direct and personal experience with severe mental illness.

6. Members of IRBs approving research on individuals with severe mental illness must receive specialized training about mental illness and other cognitive impairments and the needs of individuals who experience these disorders. Persons with severe mental illness and members of their families must be integrally involved in the development, provision and evaluation of this training.

7. Without penalty, a research participant is free to withdraw consent at any time, with or without a stated reason. Any time a participant terminates participation, regardless of reason, investigators will make every effort to ensure that linkgages to appropriate services occurs, with followup to assist that participant to establish contact with appropriate service providers and/or care-givers. If a participant disappears or terminates their continued consent, the investigator shall contact his/her family or others designated to receive notification and information.

8. **When participation by an individual in a research protocol is completed, participants and/or their families are entitled to be informed of results as soon as this information is available, to have the opportunity to receive feedback concerning their individual participation in the protocol, to critique the protocol, and to provide input concerning possible additional research.**

9. **All participants in research protocols involving the assessment of new medications will be provided with opportunities by the investigator for a trial on the medication being studied, so long as other research on the new medication has demonstrated potential safety and efficacy.**

10. **All individuals who have benefitted from the administration of experimental medications in research will be provided continual access to the medication by the investigator without cost until a source of third party payment is found.**

Mr. SHAYS. Thank you, Ms. Flynn. I'm sorry we've been pushing you a bit. Dr. Lurie, we'll be able to come back. And then you can tell us about Africa. And then we'll start our questioning. We have two votes, and we'll be back after that.

[Recess.]

Mr. SHAYS. The subcommittee will come to order. Dr. Lurie.

Dr. LURIE. Yes. Thank you very much. I just want to talk briefly about the Africa, Asia, Caribbean vertical transmission studies. To start off by just making very clear——

Mr. SHAYS. Let me just—I'm sorry. First, some of you need to be on your way by when?

Mr. CAPLAN. Twenty of.

Mr. SHAYS. Twenty of? OK.

Mr. CAPLAN. But I have a substitute behind me.

Ms. FLYNN. I do, too.

Mr. SHAYS. Well, you know what, I'm not going to have substitutes. We'll just deal. You can stay later?

Dr. LURIE. Excuse me?

Mr. SHAYS. You can stay later?

Dr. LURIE. I can.

Mr. SHAYS. OK. Why don't we just deal with the issue, then, that I'm finding absolutely fascinating. The local institutional review boards are licensed by whom?

Dr. WILFOND. The institutional review boards usually will have to file what is called a multiple project assurance with the OPRR at universities or hospitals.

Mr. SHAYS. What happens if the OPRR isn't involved?

Dr. WILFOND. Well, generally for any sort of large institution like a university it will be.

Mr. SHAYS. No, no. You've already told me under two circumstances where there's basically no review.

Dr. WILFOND. Correct.

Mr. SHAYS. Yes.

Mr. CAPLAN. The OPRR is not always involved.

Mr. SHAYS. They're only involved if Federal dollars are involved.

Mr. CAPLAN. Or IRBs if there is a new medical innovation that doesn't involve a drug or device that—the FDA is triggered there. And it has to be, I might add, for interstate commerce. If it's a new innovation in surgery, rehabilitation medicine, nursing, where there's no drug or device, there is no necessity of IRB review or OPRR connection or any review at all unless there is some commercial purpose involved and unless this work is being done at an institution that is getting NIH money for other purposes. So if it's privately funded within the State, no commercial purpose—a good example, by the way, Mr. Congressman, would be the Baby Fay baboon transplant. That looks pretty experimental—technically did not have to be reviewed by an IRB. It was privately funded, not done for a commercial purpose.

Mr. SHAYS. Now, these IRBs are commercial or not commercial? I'm not clear on that issue. At bottom line first, they don't have to be licensed?

Mr. CAPLAN. No.

Mr. SHAYS. Unless they might have to be reviewed if they are involved with the Institutes of Health.

Mr. CAPLAN. Correct. And they have regulations pertaining to their composition from the Code of Federal Regulations that require, I think, a minimum of five people, one lay person to be involved—and that lay person represents the community, although the community——

Mr. SHAYS. Do they have to register with some national board?

Mr. CAPLAN. The NIH, basically.

Dr. WILFOND. Or the FDA. So for example, these for-profit IRBs are almost exclusively——

Mr. SHAYS. Do they register with one or the other or both?

Dr. WILFOND. They could do both.

Mr. SHAYS. Do we know how many there are out there?

Mr. CAPLAN. No, we do not.

Ms. FLYNN. No.

Mr. SHAYS. This is getting a little silly.

Mr. CAPLAN. No, we do not.

Ms. FLYNN. It's very unregulated.

Mr. CAPLAN. And the definition of community member could be a community member in which the research is being conducted or 10 States away.

Mr. SHAYS. Dr. Lurie, do you want to comment on this?

Dr. LURIE. No. I think just to make a point that the IRBs have too much "I" and not enough "R." I mean, there's too many people from the institutions themselves and reviews that are occurring, are occurring much too quickly. I mean, these people are spending 1, 2 minutes on a proposal many times. But I think that, as pointed out, the financial incentives here are very powerful. And I do think there's a role for some regulation of this.

Mr. SHAYS. OK. Explain to me the whole concept of commercial IRBs.

Dr. WILFOND. Maybe I could try this again a little more carefully.

Mr. SHAYS. Yes.

Dr. WILFOND. I think Peter is right, that even within institutions like universities, there may be some conflicts of interest. But the point is that if a person is in private practice, they don't belong to any institution, the FDA still requires a review by an IRB. So where that IRB comes from is usually somebody who has set up their own IRB, files their own forms with the FDA, calls themselves an IRB, and then receives money from the investigators who want them to review their projects.

Mr. SHAYS. Are those what are referred to as commercial IRBs?

Dr. WILFOND. Yes.

Mr. SHAYS. OK. What is a non-commercial IRB?

Dr. WILFOND. A non-commercial IRB would be an IRB from an institution like a university or a hospital that would be reviewing all the projects within there. They would also have their own conflicts, but they won't be as egregious potentially.

Mr. CAPLAN. It's important to point out, too, about the institutionally based, which is university and hospital 99 percent of the time, IRBs—that they don't get paid and don't receive any money.

Ms. FLYNN. They're volunteers.

Mr. CAPLAN. They are volunteers who then work as overhead—that's where those overhead fees that the NIH charges and puts onto its grant. So there's no payment. And what you've got is some

very hard—I don't want to just beat up on the IRB members—you've got some very hardworking volunteers who are asked to carry a ball that in the commercial sector they would be paid fairly well for.

Mr. SHAYS. Any questions? Again, Dr. Caplan, you need to leave in about 7 minutes. Dr. Wilfond, you need to leave when?

Dr. WILFOND. I don't leave until 5 o'clock.

Ms. FLYNN. As soon as possible.

Mr. SHAYS. As soon as possible? OK.

Ms. FLYNN. Yes, sir. Thank you.

Mr. SHAYS. Do you have any comment you want to make before, and I'll just let you get on your way?

Ms. FLYNN. Beyond the comments that I was making in my statement in the record, I just want to reinforce the concerns that are being expressed about the IRB procedures. I think the IRB is the crux of protecting human subjects. And it is enormously variable across the country. And I think we have been very slow to recognize the training needs at IRBs, to recognize the potential importance of looking at community participation as more than just fellow physicians in the same hospital or fellow members of the same research community.

And that some of the issues we're hearing about commercial IRBs are particularly important. Because to the degree that you can buy approval—or the appearance is there, that you can buy approval—to that degree is public trust in the IRB process tremendously diminished. So I appreciate the chairman's raising these subjects and the time and attention that has been devoted to it is not beyond what is needed. And I think we've just begun a dialog that I hope will continue.

Mr. SHAYS. I thank you. And I do recognize that we have kept this panel extraordinary late. I apologize. And we've had lots of interruptions. We would have been out hours ago without the interruptions. So I do apologize. Ms. Flynn wants to get on her way. Should we let her get on her way?

Mr. TOWNS. You can put it in writing to me.

Mr. SHAYS. Sure.

Mr. TOWNS. You made a comment earlier that I'm very concerned about in terms of mental patients, in terms of the competency, in terms of privacy and all that. And I would like for you to sort of give us something in writing as to what you think we might be able to do to protect them. For instance, especially with the medication that they're getting. If it's helping them, and all of a sudden the medication disappears—and I guess sometimes it's probably the cost factor as the reason why they are not able to get it. So I would like for you to give us some suggestions. Because I think some of these things are going to require legislation.

Ms. FLYNN. I appreciate that, sir, and would be glad to provide you with some concrete and specific suggestions in writing.

Mr. TOWNS. Right. Thank you.

[The information referred to follows:]

NAMI

July 6, 1997

The Honorable Edolphus Towns
2232 Rayburn House Office Building
Washington, DC 20515

Dear Representative Towns:

At the May 8, 1997 hearing, "Oversight of the NIH and FDA: Bioethics and the Adequacy of Informed Consent," you made the following request during my testimony:

> *Please describe the ways to protect mentally ill research participants in terms of informed consent and how to maintain a healthy climate in understanding the nature, risks and benefits of the research in which they are involved.*

I greatly appreciate this opportunity to supplement the written and oral testimony I provided to the Subcommittee. My written response to your request follows.

(1). **Research participants with severe mental illnesses should be fully and continually informed, to the maximum extent possible, about the potential risks and benefits of the research, and their continuing desire to participate in the research should be evaluated and strongly considered throughout the research process.**

Brain disorders such as schizophrenia, manic-depressive illness, major depression, obsessive-compulsive disorder and panic disorder are frequently episodic in nature and fluctuate in terms of severity and duration of symptoms over time and from person to person. Hence, individuals who suffer from these disorders may experience lengthy periods during which they are perfectly capable of understanding the nature of research and providing informed consent to their participation in research, followed by periods during which their symptoms are exacerbated and they are incapable of such comprehension or consent. These fluctuations may particularly occur during research on experimental drugs. Consequently, it is critically important that the researchers recognize and take steps to ensure that individual research participants are provided with information about research they are participating in on a continual basis throughout the protocol. Moreover, informed consent should be viewed not as one-time phenomena but as a process that should continue throughout the protocol, and particularly during periods of change in the protocol or in the condition of the individual research participant.

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The severity of psychiatric symptoms may render individuals unable to fully comprehend the nature of research or to provide informed consent at certain stages of research protocols. In these instances, the following mechanisms for protecting the well being of individual research participants should be considered. These mechanisms should particularly be considered for research that is potentially risky for those who participate, or research which is potentially of limited direct benefit to those who participate.

- **Ask the research participant to identify a family member or someone else he/she trusts to assume responsibility for protecting his/her well being in the event of incapacity during the course of the research protocol. This is particularly important when the research is considered to be "greater than minimal risk."**

Legal mechanisms such as advance directives and assigning health care proxies are becoming increasingly important in the clinical provision of health care services. We recognize that these mechanisms are currently less frequently used in the context of research. However, even if a formal advance directive is not possible, researchers should strive to identify, with the research participant, family members or others concerned and capable of monitoring and protecting the well being of the participant in the event of incapacity. When such individuals are identified, the researcher should assume responsibility for keeping them informed about the nature of the research and the health status and well being of the participant throughout the protocol.

- **Assign an individual not directly involved in the research to function as a research monitor, with specific responsibility for monitoring and protecting the well being of research participants with severe mental illnesses or other cognitive impairments.**

Institutional Review Boards (IRBs) have primary responsibility for overseeing research and ensuring that research protocols are conducted in an ethical manner, with adequate protections for vulnerable research subjects. However, since IRBs are not involved in research on a day to day basis, they may not always be capable of adequately carrying out these responsibilities. One way to address this is to assign an IRB member, or someone outside the IRB but with responsibility for reporting to the IRB, to function as a research monitor. This person would function as an ombudsperson or liaison between the IRB and individual research participants, and would be particularly called upon when questions arise concerning capacity of individual research participants, when there are no family members or others assigned or available to function as surrogate decision makers.

- **Pay close attention to verbal or non-verbal signs or cues that indicate the desire of individuals to continue or discontinue their participation in research protocols. Research participants with severe mental illnesses may be capable of indicating assent to their continuing participation, even when they are incapable of providing informed consent.**

Too often, the determination that an individual is incapable of providing informed consent results in the complete disregard of that individual as a viable participant in the research decision-making process. In fact, many individuals may be capable of demonstrating their wishes and concerns verbally or non-verbally, even when they are in extreme psychiatric distress. Family members and others close to these individuals may be particularly capable of ascertaining their wishes. Hence, researchers surrogate decision-makers, and others entrusted with monitoring the well being of research participants should be strongly encouraged to continually communicate with individual research participants and to pay close attention to attempts by these individuals to communicate their desires concerning research participation.

- **The assessment of an individual's capacity to provide informed consent to participation in research should be carried out by someone other than the principal researcher or those directly involved in the research.**

Although most researchers are concerned about the well-being and best interests of those who participate as research subjects, their ability to objectively assess the capacity of subjects to provide informed consent may be compromised by their interests in ensuring that the research proceeds in a manner as free of complications as possible. Hence, we strongly recommend that capacity assessments be performed by qualified individuals who do not have a stake in the outcomes of the research and can therefore carry out these responsibilities in as objective and unbiased a manner as possible.

(2). Research participants should be closely linked to appropriate clinical care during their participation in research and, when appropriate, after their termination from the research protocol.

As discussed in our written and oral testimony, research on new medications and other types of research in the field of psychiatry is currently often conducted on an outpatient basis. It is far more difficult to monitor the daily progress of individuals on an outpatient basis than on an inpatient basis. Hence, researchers must be particularly vigilant to monitor the clinical well being of individual participants, including signs of relapse, throughout research protocols. We recommend the following steps for consideration.

- **Develop systems for monitoring the clinical well being of individual research participants. These systems should include mechanisms for responding to crisis situations or individuals in clinical distress on a 24-hour basis. Strict attention should be given to concerns expressed by family members or others involved in the lives of the research participants on a daily basis.**

Many research protocols evaluating potential new medications for the treatment of brain disorders such as schizophrenia require individuals to be withdrawn or "washed out" from the medications they previously took. During these periods, individuals may be particularly vulnerable to relapse. Researchers must adopt clinical mechanisms for responding quickly and effectively to individuals in psychiatric crisis. The responsibility of researchers extends beyond the research itself to maintaining the clinical well being of individual research participants.

- **Researchers must assume responsibility for linking research participants to appropriate clinical care after research protocols terminate particularly when individuals terminate their participation prematurely or in a state of clinical vulnerability.**

During periods of crisis or exacerbation of symptoms, individuals with severe mental illnesses sometimes deny their need for psychiatric treatment or terminate their participation in treatment. Although research is not the same as clinical care, individuals may refuse to continue their participation in research or stop meeting the criteria for continued participation during periods of relapse. At these times, these individuals are particularly vulnerable to the most devastating manifestations of severe, untreated mental illnesses, including homelessness, involvement with criminal justice systems or even suicide. Researchers must be aware of these potential consequences and should take whatever steps are necessary to link individuals with appropriate care after they terminate from research protocols.

- **Individuals with severe mental illnesses who participate in studies of potentially effective new experimental drugs should have access to trials on those medications even if they are assigned to groups that are given placebo or non-experimental drugs.**

- **Research participants who respond favorably to experimental drugs should be given continuing access to those drugs even after their participation in the research protocols is completed.**

Insurance companies and public programs such as Medicaid typically do not pay for experimental drugs. Therefore, there are no assurances that individuals who respond

favorably to experimental drugs in research protocols will be afforded continuing access to these medications. We strongly believe that individuals who demonstrate the courage and commitment to participate as research subjects should be given continuing access to beneficial medications until these medications are approved for third party reimbursement.

(3). Institutional Review Boards (IRBs) evaluating research protocols on severe mental illnesses should be knowledgeable about these disorders and the needs of people who suffer from them. Additionally, IRBs should be significantly comprised of representatives who are not professionally affiliated with the research institution conducting the studies under review.

As stated above, IRBs have primary responsibility for evaluating research protocols and monitoring the well being of those who participate as human subjects in these protocols. It is not clear that IRBs have always been able to function with the degree of independence and expertise necessary to carry out these roles. Consequently, we recommend the following steps.

- **IRBs evaluating research protocols on severe mental illnesses must include consumers, family members, and others knowledgeable about these disorders and their impact on those who suffer from them. IRBs should also include adequate multicultural and ethnic representation, including representatives of ethnic or cultural groups prominently included as research subjects.**

- **Members of IRBs evaluating and monitoring research on severe mental illnesses must receive training about these disorders and their impact on those who suffer from them. Whenever possible, persons with severe mental illnesses and their families should be included in the design and implementation of this training.**

Once again, in behalf of NAMI, I greatly appreciate the opportunity to offer additional information to the Subcommittee. Please do not hesitate to contact me with any questions or if I can be of further assistance.

Sincerely,

Laurie M. Flynn
Executive Director

Mr. SHAYS. And if the gentleman will yield. Dr. Caplan, we do need on the record one question and then you can have someone who was sworn in take your place. And we will honor that. The question I need to ask you is, in what ways do you feel that the FDA's waiver of informed consent would permit DOD to use PB and botulism toxin vaccines on Gulf war troops was ill-advised or unethical?

Mr. CAPLAN. I think the handling of the waiver with respect to the troops was unethical in three ways. First, I think they did not demand and insist upon followup, so that people who were exposed to these substances who were de facto, acting as subjects or even guinea pigs, would know whether or not there were harms or problems that arose, which may have happened now in terms of Gulf War Syndrome. I'm not sure that's true. At least they failed in the obligation that was owed to followup. They failed in the obligation to disclose what was done to these troops. You were asking the FDA in the previous panel, were you satisfied that they were in compliance with what the agreement was?

Well, I will say that I think they failed dismally and they have not—the Defense Department. Those military agencies did not do what they needed to do to, after the fact; inform people when they were exposed to innovative or experimental substances.

The last area of failure is, there's still been no formulation of a policy about what to do with respect to research on our troops. We don't have it today. We didn't have it 6 years ago. And I find it incredible that we have not had more than an interim rule to guide us with respect to research in the military.

Mr. SHAYS. And clearly we've had enough time.

Mr. CAPLAN. I would say we've had more than enough time.

Dr. WILFOND. Can I just add something?

Mr. SHAYS. Sure.

Dr. WILFOND. I think it was not convinced this morning that they ever gave a clear reason why it was not feasible to have asked for consent in the first place. Presumably, if you asked the soldiers, you may be exposed to nerve gas, this medication may help you but we really don't know, and we would like to do a project, would you like to participate, most would probably say yes.

Mr. CAPLAN. We took a lot of testimony at the Presidential Advisory Committee on this matter.

Mr. SHAYS. Yes.

Mr. CAPLAN. And it was summed up fairly well by one of our people who came to testify to us who said, if someone is shooting very large bullets at you which may be filled with biological weapons, the likelihood of you refusing an antidote is zero. So that we could assume that most people would, in fact, have taken the opportunity to get the best protection possible.

Mr. SHAYS. Yes.

Mr. CAPLAN. I wouldn't deny it. But the opportunity to ask was there. And even if it was difficult due to the quick mustering up of forces, after the fact notification is an absolute—it's just something that has to be done.

Mr. SHAYS. Yes.

Dr. WILFOND. But my point is that there's still no—it's not clear that they couldn't have done it ahead of time either.

Mr. SHAYS. Dr. Caplan, you've been terrific to wait so long. Did you want to ask him a question before he left? Yes.

Mr. TOWNS. Yes. This whole thing about ethical standards, there seems to be some disagreement on the meaning of the term. Some people think it means having standard operating procedures to review proposals. And other people think it means that the contents of the proposal should be reviewed to determine whether they meet some kind of moral standards. Can you tell me what you believe the requirements are for ethical standards in reviewing research proposals?

Mr. CAPLAN. Well, I'll try to answer that simply, Congressman Towns, by saying this. I think the job of the IRB in terms of ethical standards is to make sure that comprehensible information is given to the person so they can use their values to decide how they want to deal with risk and benefit. So the real moral principle that has to guide what the IRB is doing with the informed consent forms and all the rest of it is, can we make it so that we empower the person to be able to make a choice. The problem is that we put a lot of weight right now in our review on the front end, what's on paper, what happens at the start.

And there's very little in the middle and at the end whereby we go back and say, did you understand it, do you think we picked up the right issues, are we doing our job as committees, as people trying to empower you? But the moral principle, I would say is, empower the subject to make a choice. That's really what the job is of these IRBs, public, private, whatever they are supposed to be. They are trying to let people make choices according to their best values. Not everybody will agree.

There's no right answer about when is it too risky, when is it too dangerous, is it worth the benefit for me? But you do need information and you do need time and you do need to make sure that the person giving you that information is giving you all your choices. That's what those committees have to do. And I don't think they're doing it as well as they ought to.

Mr. TOWNS. Dr. Wilfond, your comment?

Mr. SHAYS. Thank you, Dr. Caplan.

Dr. WILFOND. Well, actually, I would take it a little further——

Mr. SHAYS. And let me just—excuse me. We will be having join us Dr. Jonathan Moreno, who was sworn in, I believe. Is that correct?

Mr. MORENO. I was.

Mr. SHAYS. Yes. And welcome.

Mr. MORENO. Thank you.

Dr. WILFOND. Yes. I think at least for children the IRBs are expected to do much more than just make sure that people have information. They are supposed to make some sort of judgment about the balance of the benefits and the risks. And the regulations are very detailed in terms of the various categories of benefits and risks. I think one of the challenges is that for research that is identified of being no direct benefit can only be approved if it—and these are the exact words—"if it is a minor increase over minimal risk."

The problem is, it's not clear what counts as minor increase over minimal risk. And many medical journals or ethics journals are

spent discussing these issues, of what counts as a minor increase over minimal risk. So I think there is really a need to conceptual clarity to be improved to allow the IRBs to do this better.

Mr. TOWNS. All right. Thank you.

Dr. LURIE. Yes. Let me add to what Dr. Wilfond is saying. Obviously, adequately informing people is critical, but it's at times not sufficient. So as bad as the informed consent form was in the Alaska study, it couldn't have made the study ethical. So an unethical study is an unethical study. And the IRBs need to stop those from proceeding regardless of how good the informed consent form is. And the same thing, I believe, is true in the African studies, which we'll get to later. There may indeed be problems with informed consent. We haven't looked at all the informed consent forms yet. But there is no informed consent form that could satisfy me that these studies are ethical. The study is unethical by design. And you can't informed consent your way out of that.

Mr. TOWNS. Right. Let me just ask one more question, Mr. Chairman. May I?

Mr. SHAYS. Yes.

Mr. TOWNS. I'm concerned about when these studies go wrong, they seem to be conducted on poor people, minorities in particular, and in some instances their children. I wonder if one factor considered in the approval process is the economic status of the people to be studied. Wouldn't the economic status have a bearing on nutrition, other factors that could influence the outcome of the study?

Mr. MORENO. Perhaps I could address that.

Mr. TOWNS. Sure.

Mr. MORENO. Incidentally, I work at the Health Science Center at Brooklyn——

Mr. SHAYS. Yes. Would you——

Mr. MORENO. My name is Jonathan Moreno. I'm a professor of bioethics at the Health Science Center at Brooklyn State University of New York.

Mr. SHAYS. OK.

Mr. TOWNS. That's a very important place, Mr. Shays.

Mr. SHAYS. It is a very important place. Not the most important, but a very important place.

Mr. TOWNS. Thank you.

Mr. MORENO. It's near Connecticut, at least. We deal with this issue all the time at an institution like ours. As you know, we have a large minority population and many subjects who don't have economic means and are vulnerable. The one ethical principle that has, I think, been the most difficult to interpret and apply in our system that came from the National Commission in the late 1970's is justice. And according to the National Commission, justice in the context of the use of human subjects in research means that you don't overburden any population in the society with respect to research participation, and that you also, importantly, make sure that the fruits of research are available across the board, through the whole society.

That's really very hard to do, partly because when people don't have economic means they may not have the ability to participate in research because they are, for example, taking care of older people or younger people, or they don't have the money to come to the

center to be part of a study, or because of the possibility that they could get sick from being on a drug, and to be taken off-line from work or taking care of those other people, could represent a serious practical obstacle to being in a study.

So there are problems on both ends, I would say, Congressman. One problem is that, yes, it's true that people who are in the position you've described may be more vulnerable. At the same time, we aren't very good at recruiting them to research that could benefit them or could benefit other people in their circumstances.

Mr. TOWNS. Yes. Would you like to add anything to that?

Dr. WILFOND. It goes—he's correct. It goes both ways. It's a problem both on the side of recruiting appropriate subjects. And in fact, the NIH has really tried over the last few years to try to increase the enrollment of minorities and women in studies. I think there also is a problem of inappropriate recruitment. One problem that I see which I alluded to in my comments has to do with the issue of reimbursement for money. We were asked at one point to review a study on volunteers. Well, why didn't they get 8 hours of general anesthesia for the cost—for which they would be paid $1,000. And we thought that this was potentially risky. And we thought that the only people who would be willing to do this would be people who really needed that money.

And so we actually did not approve that study. But for precisely that reason, that, as Peter mentioned, it's not just the risks but what will make people do it. And often it's for the money.

Dr. LURIE. I think you're raising a very important point. And let me emphasize it by saying that I think your observation is accurate, that I think the anecdotes that are being brought up today illustrate your very point. I mean, I've talked about injection drug users. I've talked about poor people in developing countries. People talk about people with mental illness. People in the military whose ability to refuse participation is limited. I mean, I think it's absolutely consistent with your point.

Let me illustrate it perhaps by comparison. In the needle exchange study, there was no hepatitis B vaccine, at least in the initial phase, planned to be administered in any important way to the subjects. And so the idea was to watch people and see whether or not they got hepatitis B even though there was a vaccine. Now, let's imagine a study of young infants in which the question was did they get tetanus or not, and the researchers just kind of watched to see if they did without providing them with tetanus vaccine.

It's inconceivable. Nobody would have done anything like that. But when it's injection drug users I think somehow there's an acceptance of the poor quality of medical care that often is afforded to these people. The same thing is true with regard to the degree of evidence that we now seem to require of needle exchange programs. There are no randomized controlled trials of whether or not condoms work to prevent the transmission of HIV.

Yet suddenly, primarily for political reasons, people dredge up the idea that we need randomized control trials for needle exchange. No one dreams of a randomized control trial of condoms for gay men, for example, because as discriminated against as gay men, in fact, are in this country, they are still better organized

than drug users. So I think both of those points really emphasize what you say. And I think in many ways that's what's operating the African, Asian and Caribbean studies where there is in fact an incentive now.

If we're saying we only have to provide the standard of care that exists in these impoverished countries that can't afford our overpriced drugs, what we're saying is, there's really an incentive for people to go overseas and find the place with the least medical care, and then we can get away with doing nothing. Provide getting a bunch of information that may or may not benefit them. And we may very well take the results back to our countries ourselves where our people will benefit. That is exactly—so I highly endorse the concern that you're raising.

Mr. TOWNS. Last question and then I'm going to——

Mr. SHAYS. No, that's fine. We want to make sure that, Dr. Lurie, that you get to talk about Africa.

Mr. TOWNS. Africa. Yes. Maybe this can lead him into it. I have this feeling—I'm not certain—but based on the information that I've received, and reading in terms of the way in many times these programs are structured, in terms of research programs are structured, that you have a physician in a foreign country doing research. And he's so involved and wrapped up in his research, that he's really not paying attention to some of the other symptoms of the patient that might give him signs that certain things are happening. But they just continue with their research, because, after all, that's what I'm into, my research.

As a result, in many instances, patients that are lost should not be lost. If this patient had a physician that was responsible for the medical care while the other person is responsible for the research, that it seemed to me that some of the things that occur might not occur. Now, am I right in my assumption that this is the structure, when I have my patients and I am involved in the research—and, of course, you do not have a physician that's responsible for the day-to-day health.

Dr. LURIE. Well, Dr. Jay Katz—that's for you, Congressman Shays—a nice mention of Connecticut——

Mr. TOWNS. Right. Yes.

Dr. LURIE [continuing]. Has the notion of a physician researcher, people who have, in fact, these dual responsibilities and should really take both of them into account when acting as researchers either in this country or in a foreign location. And I think that is the way that we need to be thinking about it. Unfortunately, there's been a kind of a specialization of function in which people consider themselves to be one or the other, and say, well, that's not my job, I'm doing the research here, somebody else is providing clinical care, that's not my problem.

So I think that is exactly right. The problem, in fact, becomes, as I indicated in my testimony, that sometimes there is, in fact, a conflict or an apparent conflict between what the researcher thinks that he or she needs and what it is that the people in the trial need. Those women who are HIV positive and pregnant and stand a 25 percent at least chance of delivering an HIV positive baby, they don't need research. Those women need AZT.

Mr. TOWNS. Yes.

Dr. LURIE. It works. Not 100 percent, but it works. It works better than most other things we have to prevent HIV in this country. It works. That's what they need. They don't need more research. Yet, somehow what we heard a lot of this morning was the idea that yes, it's true that these women might be placed at risk, but there are going to be future benefits.

And one of the clearest principles that came out of the Nazi experiments during World War II was the notion that you can't place individuals at risk in the present for potential future benefits, that the people in the study have their own integrity, that they have to be protected in and of themselves, and that you can't justify any old research simply by saying, well, we're going to get good information from this and other women like this are going to benefit in the future. It may never happen, and it's a slippery slope to some very, very dangerous places.

Mr. MORENO. Clinical investigators are often called double agents in the bioethics literature.

Mr. SHAYS. Say that again.

Mr. MORENO. A double agent problem is the problem that Congressman Towns alluded to, namely that, "I've got a grant and I'm doing some research, and I'm also using some patients in the study who in a certain sense may assume that I'm primarily concerned with their individual care." And while I may indeed be concerned with their well being, I also want to get some data. That's a problem, though, not only on the side of the physician investigator—I worked for the President's Advisory Committee on Human Radiation Experiments, and we did focus groups with hundreds of people who are in studies.

We found that even through they were theoretically and documentedly informed that this was primarily research, that it was not intended to benefit them—and most research is not intended to benefit the subject—nevertheless, they had a hard time integrating that information. It's very hard to face that when you're sick and you're looking for an answer. So this is not something perhaps too amenable to legislation. It's human psychology. It's often very difficult for people to accept that they're making a big personal investment of both time and hope. And it may not help them.

We did find that as people went on through the course of their disease, they were more willing to accept that their participation was not going to help them, but might well help somebody else. We also find—I want to point this out—from the point of view of the person who is sick and in a study—this work we did for the Advisory Committee on Human Radiation Experiments—we also found that a very important motivation for people to be in studies is that they trust the institutions that are sponsoring the studies.

This is a guy in a white coat who has a lot of knowledge and a lot of power and a lot of authority. This is a great institution. Look at these buildings. Look at the labs. Look at all the nurses. This is an important place in my community—the State University of New York. Surely what they're doing is going to be good for me. Trust is a very—what I'm saying is something that you already know: trust is a very delicate thing.

Mr. SHAYS. That's very true, Doctor, and very important to point out. Dr. Lurie, how long do you think it will take you to—because I do have some follow questions, and we're going to go to a vote soon. But I do want you to deal with Africa. But give me a sense of how long it will take you to describe the clinical research?

Dr. LURIE. I'd say probably 3 minutes.

Mr. SHAYS. Let's do it.

Dr. LURIE. Let me just emphasize from the beginning that there is nothing in the position that we have taken that states that we are opposed to randomized, controlled trials. And there's nothing in our statement that says we are opposed to placebo controlled trials per se. We are in this particular situation. But not in general. We're also not opposed to international research. What we are opposed to is double standards. And we don't like a double standard where, for example—there are two American studies in which AZT is provided, or something similar to AZT is provided to the treatment groups, yet the minute people go overseas, it's like they check their research ethics at the customs desk. Only 1 out of the 16 studies that are being done in developing countries provides AZT to all treatment groups. That's a double standard.

And it is that particular one study that in many cases illustrates the inconsistency and lack of coordination that have plagued this particular set of studies. How can it be that the National Institutes of Health is funding a non-placebo controlled trial of these mother-to-infant transmission prevention interventions in the very same country that the Centers for Disease Control is conducting a placebo controlled trial?

How can that be? And I think that perhaps the most important thing that I heard, at least with regard to the African studies or Thai studies, was what Dr. Varmus said this morning, which was, when asked that very question by Mr. Kucinich, he responded that the placebo controlled trial was "not the only way to achieve results." That's exactly right. It is not the only way to achieve results. And the difference between the method that has been chosen by the CDC in Thailand and the NIH and the CDC in other places is not the only way to achieve results.

Unfortunately, one result that it will achieve is that if you add together the American and the foreign-funded studies, there will be 1,500 HIV positive babies in this world which need not happen. Even though we have a big research infrastructure that goes in, it doesn't cost that much to provide AZT. In many cases you get it free form the drug company. And yet we're effectively staring those women in the eye and saying, no, we need a placebo controlled trial. And consequently there are 1,500 HIV positive babies that will exist within a couple years from now when they need not.

The final point I wanted to make was about the IRBs. And we heard a lot about how this all went through the IRB in these local countries. I think that Dr. Wilfond, Dr. Caplan and others spoke very well to the problems of IRBs in this country.

Mr. SHAYS. I'm not clear. There are IRBs in other countries just like in the United States?

Dr. LURIE. Well, whether it's reasonable to call them per se an IRB, I'm not exactly sure. I'm sure they are not constituted necessarily with the kinds of regulations that we have in this country.

Mr. SHAYS. So you're basically talking about the health ministries of the country?

Dr. LURIE. In many cases there is some kind of review committee that will review this. I mean, myself, I've conducted quite a bit of research——

Mr. SHAYS. Is that set up by international agreement, World Health——

Dr. LURIE. My understanding is that it's understood that studies like this will be reviewed, but there is not the same kind of detailed information about who will sit on these things. I don't believe that there is a requirement——

Mr. SHAYS. Let me just say something. I'm truly exposing my ignorance in this area. But it does blow my mind. I mean, the value that someone like I bring to this is, I know nothing.

Dr. LURIE. Yes. That's right.

Mr. SHAYS. But I come with a clean slate. And there are things that just frankly have blown my mind about what I've learned today. Because I made assumptions. I made assumptions about a lot of things that are very different than what I've learned. And so there will definitely be followup at the urging of my ranking member, as well. This is an issue we're going to get into with a lot more interest than we've shown in the past. Why don't you finish your point.

Dr. LURIE. Well, you know, I think you are exactly the right person to be making a judgment about these kinds of things. I mean, the scientists are themselves too close to the problem. And I think that's a lot of what we heard this morning, that there are people standing up and basically defending either their government institution or otherwise their university. We've heard a lot of that. I think it's the kind of distance that a sort of naive observer like yourself has to offer.

And the common sense thing is no; 1,500 lives that could be saved. Why not do it? Why not do it if you can get data that are good enough to make decisions, which even Dr. Varmus himself says are good enough to make decisions. I think they're too close. I think that's part of the problem. Anne Marie Finley used the expression from a song recently: "blinded by science." And I think that's part of what the problem is. It's too much on the science, not enough on the broad of social and ethical contexts of things.

Mr. SHAYS. OK.

Dr. LURIE. My final comment with regard to IRBs, then, is, can we trust the IRBs overseas? And as somebody, as I said, who has done quite a bit of research in Africa and Asia, I've used IRBs in those countries myself. I have no confidence in the fact that they say that my research is OK. It does nothing for me. At least the research I have done. I am sure that the research committees, the ethics committees established for these studies, are in fact better than the ones that I have run my research through. There's nothing I can do about that.

Of course, it runs through an ethics committee in our country, as well. But if you take, for example, some FDA inspections from the period of 1977 through 1995 published here in the Cleveland Plain Dealer, the United States—there were 32 percent of studies in these inspections which deviated from protocol. And their inspec-

tions of foreign IRBs, there were 54 percent that so deviated. And with regard to the keeping of adequate or accurate records, there were 27 percent of American IRBs that had inadequate or inaccurate records. And in that same period, the percentage in foreign countries was 53 percent.

So there is reason to believe that, for starters, the very same pressures so well described by Dr. Wilfond and Dr. Caplan that exist in this country exist over there. And seeing as though these committees are much newer, they don't have the same research infrastructure, there are fewer people with formal training in ethics than exist in this country, I think it's reasonable—and the data support the idea—that ethical review over there is likely to be poor.

Mr. SHAYS. I just have about four more questions. And I can go through them fairly quickly. I don't know if the answers will be quick. But it's Dr. Moreno.

Mr. MORENO. Moreno.

Mr. SHAYS. Moreno. I'm sorry. Dr. Moreno. How is data collection and monitoring of animal subjects more extensive than required for human subjects? First, is it? And if so——

Mr. MORENO. I think it is. I sat on an animal care and use committee in my school a number of years ago. So my memory may not be fresh. But as I recall—and I hope other people will correct me if I'm wrong—there is annual auditing of animal care and use committees. And I believe that they are unannounced. There is at least regular auditing of animal care and use committee records. And I believe they are unannounced. In the case of human subject review committees, I believe that they can take place every several years and they are announced.

Mr. SHAYS. Well, we will be looking into that. But the bottom line is——

Mr. MORENO. The bottom line is there is less regulation for human subjects than there is for animals, in that sense, in the sense of auditing by a Government body.

Mr. SHAYS. OK. Dr. Wilfond, how would a functioning HHS ethics advisory board provide greater oversight of informed consent in the United States? One, should we allow that board to continue to just sit there or should we activate it?

Dr. WILFOND. Well, I think it should be activated. I think there are two things that having a functioning board—a permanent board could do. One would be, as I alluded to, trying to help over time develop some more conceptual clarity about how to resolve ethical issues. But I think more importantly it could be a mechanism for having one singular mechanism of oversight of IRBs and make sure that all research goes through those IRBs, make sure that those IRBs are at a community level, and make sure that the IRBs do ongoing monitoring of the research. And the only way that can be done is by having one single agency who is responsible for doing all this stuff.

Mr. SHAYS. Yes.

Mr. MORENO. Can I just add to that, also?

Mr. SHAYS. Sure.

Mr. MORENO. There are big philosophical and policy issues emerging that local IRBs may not be comfortable in settling. For example, the use of AZT in pregnant women, which I dealt with in

Brooklyn a few years ago. That also could be subject to an open public review that would take some of the moral pressure off the local institutions.

Mr. SHAYS. Do you have anything to respond to those two questions?

Dr. LURIE. No.

Mr. SHAYS. We have a vote. I think what we're going to do is call it quits here. You have definitely encouraged this subcommittee to move forward as this is an extraordinary issue. I've made assumptions about the local boards and their powers in oversight. I've made assumptions about what the FDA has done or hasn't done. I've made assumptions about the Institutes of Health that are quite the same as I thought. And I know everybody is wrestling with this issue. But it strikes me that we'll be able to focus in a little bit more. I'll be able to do some homework in the meantime to make sure that we don't let the first panel get away without asking some of them these questions. So with that—do you have anything to add, Mr. Towns?

Mr. TOWNS. No. I think it was terrific in terms of information that they were able to share with us. I really appreciate it. Thank you very much.

Mr. SHAYS. Yes. I'd just like to thank the staffs on both sides who worked close together and have provided very helpful information to prepare us and have gotten us some excellent witnesses. So thank you for coming. Do any of you just wish to say something before leaving? Is there any one last parting comment you want to make?

Dr. WILFOND. Actually, I do have one.

Mr. SHAYS. Yes?

Dr. WILFOND. Since I haven't really spoken to the issue of the studies of the AZT trials I think there's two points I want to emphasize.

Mr. SHAYS. Sure.

Dr. WILFOND. One is that Peter is correct that these studies could be done using AZT as the control, but it would take more time and it would cost more money. So essentially, the ethical question is whether or not it's appropriate to spend that time and money. And I think we need to understand that. The second thing was a comment that I heard earlier that the reason why those studies were justified is because the host countries thought it was appropriate. Well, the host country thought that Tuskegee was appropriate. So the fact that people agree in a country that a study should be done it doesn't make it ethical or unethical itself.

Mr. SHAYS. Right. That's a very good point.

Dr. WILFOND. And so, be careful about that.

Mr. SHAYS. Very good point.

Dr. LURIE. If I just may respond to that, about more time or money. You know, it is quite unclear that's necessarily so. It depends to a certain degree where the short version of AZT falls out, whether it turns out to be closer in effectiveness to placebo or closer in effectiveness to the 076 regimen. So the answer is, it depends. And again, as we pointed out earlier, oddly enough, the placebo controlled trial that is being done with four arms involved 1,900 subjects, whereas the only other four arm study which was not pla-

cebo-controlled, oddly enough, required less. So I don't think it's necessarily true. But most importantly, whatever increment in additional money is necessary to make the studies ethical should be money that we're willing to pay. if it costs double the money to do the study, as far as I'm concerned, that's money we need to spend, and we cannot afford to be unethical.

Mr. SHAYS. No, we can't. We do have to be very up front with the point that everything is an opportunity cost. And I would say it's unethical to spend money on research that may not optimize the results. Maybe it's more ethical to spend money on something that will give better results and help more people. There are lots of ways to evaluate the concept of money. I want to be very clear. I'm not disputing that you should never, whenever money is spent, you shouldn't spend it on research that isn't ethical and done properly. But we make choices in how best to allocate a resource.

Dr. LURIE. I think it's a reasonable point. But let's not forget that in this particular case, the choice involves not only money, not only time, but actually involves people's lives, which in many cases in some of the other studies that we've talked about—as terrible as they may be—you could not predict the number of deaths that were likely to ensue as the case here. If it costs double the amount of money, and 1,500 more babies are alive to see their 7th or 10th birthday because we did our studies better, I'd be willing to pay that.

Mr. SHAYS. I hear you. And I think most would. Any other comment, or should we call this hearing to a close. I guess it would be, again, appropriate to thank you all for your flexibility with all the votes we had today. And those of you who have attended and sat through this hearing, we thank you for your participation. I was thinking as we were going on that with the powers invested in me as a chairman some time, I'd like to just invite people from the audience sometimes after they've heard it, you know, at random to allow four or five, because I see nodding of head and shaking of head. And I'd love to know why you nodded your head or shook your head.

With that, we'll call this hearing to a close.

[Whereupon, at 3:10 p.m., the subcommittee was adjourned.]

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