OFFICE FOR PROTECTION FROM RESEARCH RISKS
DIVISION OF HUMAN SUBJECT PROTECTIONS

INVESTIGATION OF NONCOMPLIANCE WITH DHHS REGULATIONS FOR THE PROTECTION OF HUMAN RESEARCH SUBJECTS INVOLVING THE NATIONAL INSTITUTES OF HEALTH INTRAMURAL RESEARCH PROGRAM

FINAL REPORT

Issued
March 26, 1993

OFFICE FOR PROTECTION FROM RESEARCH RISKS
DIVISION OF HUMAN SUBJECT PROTECTIONS

INVESTIGATION OF NONCOMPLIANCE WITH DHHS REGULATIONS FOR THE PROTECTION OF HUMAN RESEARCH SUBJECTS INVOLVING THE NATIONAL INSTITUTES OF HEALTH INTRAMURAL RESEARCH PROGRAM

FINAL REPORT

October 30, 1992

Background

On July 16, 1990, the Office for Protection from Research Risks (OPRR) received allegations of noncompliance by the National Institutes of Health Intramural Research Program (NIH-IRP) with the requirements of the Department of Health and Human Services (DHHS) Regulations for the Protection of Human Research Subjects at Title 45, Code of Federal Regulations, Part 46 (45 CFR 46). OPRR initiated an investigation immediately upon learning of the allegations, which involved collaborative AIDS-related research activities in France and Zaire.

The results of OPRR's investigation are detailed in its Interim Report issued on July 3, 1991 (Attachment A). In brief, OPRR determined that the NIH-IRP system for protecting human subjects had not been adequate relative to the collaborative research activities under investigation (Interim Report, pages 10 - 14). Moreover, OPRR identified a number of systemic deficiencies in human subject protections within the NIH-IRP (Interim Report, pages 14 - 16). These deficiencies collectively constituted a failure to comply with the requirements of DHHS regulations at 45 CFR 46 and with the terms of the NIH-IRP Multiple Project Human Subjects Assurance (MPA # M-1000). Specific corrective actions were required and/or recommended (Interim Report, pages 16 - 19).

OPRR withheld final resolution of its investigation pending (a) review of records that might establish the exact nature and degree of harm experienced by subjects, and (b) implementation of required improvements in the NIH-IRP system of human subject protections. Restrictions placed on the NIH-IRP MPA effective February 7, 1991, remained in effect subject to review and approval by OPRR of a revised MPA reflecting implementation of these improvements.

Harm to Human Subjects

As indicated in OPRR's Interim Report, the lives of three human subjects were apparently shortened as the result of involvement in the research under investigation. Because the NIH-IRP bears responsibility for research utilizing its materials or involving the regulated activities of its scientists, OPRR sought to determine whether the research resulted in any additional harm to human subjects. OPRR attempted, through the U.S. State Department and the NIH Fogarty International Center, to provide for independent review of medical and research records that might establish the nature and degree of such harm.

OPRR's request to conduct an on-site review of these records was not granted by the Government of France (Attachment B). Rather, OPRR was directed to the reports of two internal inquiries (dated March 22 and June 14, 1991) which concluded (a) that applicable French regulations had been followed, and (b) that continuation of the research was legitimate. The French government subsequently provided confirmation (a) that OPRR's Interim Report had accurately characterized the above referenced harm, (b) that no other similar cases have ever been reported, and (c) that no other subjects experienced adverse affects.

The Government of Zaire did not respond to OPRR's request to conduct an on-site review of relevant medical and research records. Although the Government of France appointed an expert to investigate the matter in Zaire, OPRR was subsequently informed by the French government that political conditions in Zaire had made it impossible for that expert to conduct an on-site investigation.

OPRR would have preferred to conduct its own on-site investigation of this matter with review of all relevant medical and research records by experts of its own choosing. It is clear that these procedures are not possible in this case. Consequently, OPRR has not been able to determine independently and definitively whether additional human subjects were harmed as the result of involvement in the research under investigation. Based on the information provided by the French government, it has been determined that no additional OPRR actions in this regard are warranted.

Required Corrective Actions

OPRR's investigation revealed a disjointed, compartmentalized system of human subject protections within the NIH-IRP. Specific deficiencies were identified (a) in the NIH-IRP's administrative oversight of policies and procedures for protecting human research subjects, and (b) in the level of understanding about human subject protections among NIH-IRP investigators.

OPRR's Interim Report (pages 16 - 17) specified four Corrective Actions to address these deficiencies and to ensure adequate protections for human subjects under the NIH-IRP MPA. The Interim Report directed the NIH-IRP to:

(1) Identify a central administrative official with authority to sign, and take responsibility for compliance with, the MPA. It was stipulated that sufficient staff reporting to this official must be assigned the responsibility of tracking and exercising oversight over all human subjects research that the NIH-IRP conducts or supports.

(2) Establish policies and procedures to assure identification, required initial and continuing review, certification, and required reporting of all human subjects research that it conducts or supports. It was stipulated that standard operating procedures to be followed by all intramural personnel must clarify the lines of authority and responsibility for all aspects of the NIH-IRP human subject protections system.

(3) Develop and implement an effective program of continuing human subjects education for all appropriate intramural staff (including intramural scientists who are not clinicians and their supervisors). It was stipulated that this program must include individual and agency responsibilities under the regulations, as well as an historical perspective and theoretical justification for human subject protections.

(4) Develop policies and procedures to bring the human subjects research activities of Extramural NIH staff under an appropriate Human Subjects Assurance of Compliance.

Current Human Subject Protections Under the NIH-IRP MPA

On July 10, 1992, OPRR approved a revised MPA (Attachment C) under which the NIH-IRP has implemented substantive improvements in its system for protecting human research subjects. These improvements include measures that satisfactorily address Corrective Actions (1), (2), and (4) above.

In addition to the various procedural improvements specified in the revised MPA, the NIH Deputy Director for Intramural Research has been identified as the institutional official responsible for human subject protections. An Office of Human Subjects Research (OHSR) has been established to track and exercise oversight over all human subjects research conducted or supported by the NIH-IRP. The OHSR has developed and begun to implement a program of continuing human subjects education (Attachment D), as required by Corrective Action (3).

OPRR has made the following determinations regarding the NIH-IRP system for protecting human research subjects:

(1) OPRR finds that current NIH-IRP human subject protections, as detailed in the revised MPA # M-1000, satisfy the requirements of DHHS regulations at 45 CFR 46.

(2) OPRR hereby removes all restrictions previously imposed on the NIH-IRP under MPA # M-1000.

(3) Pending full implementation of its human subjects education program, the NIH-IRP must submit progress reports to OPRR at six month intervals beginning April 1, 1993. These reports should summarize the activities of the OHSR during the report period and should include copies of any OHSR operating guidelines or informational materials that have been developed during that period.

ATTACHMENT A

Office for Protection from Research Risks
Division of Human Subject Protections

Findings and Required Actions Regarding
Investigation of Noncompliance with
Department of Health and Human Services Regulations
for the Protection of Human Research Subjects
Involving the National Institutes of Health
Intramural Research Program

Interim Report
Issued July 3, 1991

* * * *

Interim Report Attachment F
NIH Response dated June 21, 1991

Interim Report Attachment G
Letters from Professor Zagury and Dr. Picard
Dated June 21 and July 15, 1991

OFFICE FOR PROTECTION FROM RESEARCH RISKS
DIVISION OF HUMAN SUBJECT PROTECTIONS

Findings and Required Actions Regarding Investigation of Noncompliance with HHS Regulations for the Protection of Human Research Subjects Involving the National Institutes of Health Intramural Research Program

Preface

The Office for Protection from Research Risks (OPRR) herein presents its interim report concerning noncompliance with the Department of Health and Human Services (HHS) Regulations for the Protection of Human Research Subjects (45 CFR 46) involving the National Institutes of Health Intramural Research Program. The investigation of this matter was conducted in accordance with OPRR's responsibility (delegated by the Secretary, HHS pursuant to Sec. 491 of the Public Health Service Act) for determining the applicability of the HHS human subjects regulations and for conducting compliance oversight activities concerning them.

Final OPRR action in this matter is dependent, in part, upon completion of the Division of Human Subject Protection's (DHSP) continuing investigation into the nature and degree of any harm that may have been experienced by human subjects. DHSP is attempting through diplomatic channels to provide for independent review of relevant medical and research records, as well as access to findings of relevant local investigations.

OFFICE FOR PROTECTION FROM RESEARCH RISKS
DIVISION OF HUMAN SUBJECT PROTECTIONS

Findings and Required Actions Regarding Investigation of Noncompliance with HHS Regulations for the Protection of Human Research Subjects Involving the National Institutes of Health Intramural Research Program

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Attachments

Attachment A — Partial Chronology of Events

Attachment B — Memorandum to Acting Director, NIH from Director, DHSP, OPRR Restricting the NIH Assurance (1/24/91)

Related Documents:

- B-I — Letter from Mr. Crewdson (7/6/90)
- B-II — Memorandum from Deputy Director for Intramural Research (6/86)
- B-III — Memorandum from Acting Director, NIH Clinical Center (6/86)
- B-IV — NIH Multiple Project Assurance (MPA # M-1000)
- B-V — HHS Regulations (45 CFR 46)
- B-VI — Memorandum from Director, DHSP, OPRR (7/18/90)
- B-VII — Memorandum from Director, DHSP, OPRR (7/23/90)
- B-VIII — Memorandum from Acting Director, NIH Clinical Center (7/20/90)
- B-IX — Memorandum from Acting Director, NIH Clinical Center (10/5/90)
- B-X — Memorandum from Director, DHSP, OPRR (1/24/91)

Attachment C — Memorandum from Acting Director, NIH designating Signatory for NIH Human Human Subjects Assurances (1/39/91)

Related Documents:

- C-I — Memorandum to NIH Deputy Director for Intramural Research (1/30/91)
- C-II — Memorandum from Director, OPRR (2/1/90)

Attachment D — OPRR Charge to Group of Special Consultants

Related Documents:

- D-I — List of Background Materials Forwarded to Special Consultants Prior to Meeting
- D-II — Agenda for Meeting of Special Consultants
- D-III — List of Additional Materials Supplied to Special Consultants During/After Meeting

Attachment E — List of Special Consultants

Related Documents:

- E-1 - E-7 — Individual Reports of Special Consultants

Attachment F — NIH Response to the OPRR Report

Attachment G — Letters from Professor Zagury and Dr. Picard: June 21, 1991 and July 15, 1991

OFFICE FOR PROTECTION FROM RESEARCH RISKS
DIVISION OF HUMAN SUBJECT PROTECTIONS

INVESTIGATION OF NONCOMPLIANCE WITH DHHS REGULATIONS FOR THE PROTECTION OF HUMAN RESEARCH SUBJECTS INVOLVING THE NATIONAL INSTITUTES OF HEALTH INTRAMURAL RESEARCH PROGRAM

FINAL REPORT

Preface

The Office for Protection from Research Risks (OPRR) herein presents its final report concerning noncompliance with the Department of Health and Human Services (DHHS) Regulations for the Protection of Human Research Subjects (45 CFR 46) involving the National Institutes of Health Intramural Research Program (NIH-IRP). OPRR's investigation was conducted in accordance with its responsibility (delegated by the Secretary of Health and Human Services pursuant to Section 491 of the Public Health Service Act) for determining the applicability of the DHHS human subjects regulations and for conducting compliance oversight activities concerning them.

On July 3, 1991, OPRR issued an Interim Report (Attachment A) which identified a number of deficiencies in human subject protections within the NIH-IRP. These deficiencies collectively constituted a failure to comply with the requirements of DHHS regulations at 45 CFR 46 and with the terms of the NIH-IRP Multiple Project Human Subjects Assurance (MPA # M-1000). OPRR required specific corrective actions to ensure adequate protections for human subjects under the MPA.

On July 10, 1992, OPRR approved a revised MPA under which the NIH-IRP has implemented the required corrective actions. OPRR has determined that the current NIH-IRP system for protecting human subjects satisfies the requirements of DHHS regulations. All restrictions previously imposed on the NIH-IRP MPA are removed.

This report was forwarded on October 30, 1992, to the NIH-IRP and to Professor Zagury and Dr. Picard. The statement of response from the NIH-IRP is presented herein as Attachment E. Professor Zagury's statement of response is presented as Attachment F.

OFFICE FOR PROTECTION FROM RESEARCH RISKS
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OFFICE FOR PROTECTION FROM RESEARCH RISKS
DIVISION OF HUMAN SUBJECT PROTECTIONS

Findings and Required Actions Regarding Investigation of Noncompliance with HHS Regulations for the Protection of Human Research Subjects Involving the National Institutes of Health Intramural Research Program

May 31, 1991

Background

On July 16, 1990, the Office for Protection from Research Risks (OPRR) was made aware of allegations of noncompliance with Health and Human Services (HHS) Regulations for the Protection of Human Research Subjects at Title 45, Code of Federal Regulations, Part 46 (45 CFR 46) on the part of certain National Institutes of Health (NIH) intramural scientists (see Attachment A for a chronology of relevant events). The allegations, presented by Mr. John Crewdson in a letter dated July 6, 1990, to the NIH Associate Director for Communications (and received by him on July 13), concerned possible collaborative AIDS-related research activities in Zaire and France (see Attachment B and Document B-I).

The HHS human subjects regulations (45 CFR 46) apply to all research activities of NIH intramural scientists that involve human subjects, whether carried out domestically or in foreign countries (see Attachment B and Documents B-II through B-V). In partial fulfillment of requirements set forth at 45 CFR 46.103, NIH intramural research activities are carried out under an OPRR-approved Multiple Project Assurance of Compliance with the HHS human subjects regulations (MPA # M-1000). The regulations require that all activities of NIH intramural scientists involving human subjects be reviewed and approved by the appropriate Institutional Review Board (IRB), designated at NIH as the Institute Clinical Research Subpanel (ICRS).

OPRR initiated an inquiry immediately upon learning of the allegations on July 16, 1990. As a first step, information regarding the alleged collaborative activities was requested from Dr. Saul Rosen, the responsible institutional signatory for the NIH Multiple Project Human Subjects Assurance in his role as Acting Director of the NIH Warren Grant Magnuson Clinical Center (see Document B-VI). Dr. Rosen was unable to identify any relevant protocols within the NIH ICRS system (see Document B-VIII).

Judging the allegations to be potentially serious, OPRR took action on July 23, 1990, to protect human subjects who might be involved in any new or ongoing research.

In conjunction with Dr. Rosen, OPRR stipulated (effective July 23) that any activities involving the transfer of funds, information, or chemical/biological materials between the National Cancer Institute Division of Cancer Etiology (or its scientists) and the French institutions referenced in the allegations were prohibited, unless cleared through the NCI-ICRS, the Acting Director, NIH Clinical Center and OPRR (see Document B-VII). All affected parties were advised that any use of HHS support for research involving human subjects could occur only in accord with an Assurance of Compliance approved by OPRR.

Consistent with their obligations under 45 CFR 46.103(b)(4)(iv) and 45 CFR 46.108(c), institutions against which allegations of noncompliance have been raised are expected to provide OPRR with all information pertinent to such allegations. Accordingly, OPRR formally requested on July 23 that Dr. Rosen, as the responsible institutional signatory for the NIH Multiple Project Human Subjects Assurance, investigate the allegations and report findings to OPRR by August 10 (see Document B-VII).

Dr. Rosen investigated the allegations as requested and (after extensions were granted) responded on behalf of the NIH in a written report dated October 5 (see Document B-IX). However, OPRR found the report unsatisfactory because it failed to answer a number of questions critical to determining the validity of the allegations and raised serious concerns as to the adequacy of the NIH system for assuring protection of human subjects in international collaborative research (see Attachment B and Document B-X). Such protection is required under the HHS regulations and the NIH Multiple Project Human Subjects Assurance.

As OPRR reviewed Dr. Rosen's report and analyzed its contents, it became apparent that Dr. Rosen, as Acting Director of the NIH Warren Grant Magnuson Clinical Center, exercised authority almost exclusively within the Clinical Center itself. Dr. Rosen had no direct authority over (and little opportunity to influence) intramural scientists who were not actually conducting research in the NIH Clinical Center. The result was that the signatory official responsible (under the NIH Multiple Project Assurance) for compliance with HHS human subjects regulations on behalf of the <u>entire</u> NIH intramural program did not exercise line authority over that portion of the intramural program in which scientists operate outside the NIH Clinical Center. It became clear to OPRR that NIH's inability to produce a satisfactory report on the allegations was intimately linked to its inability to ensure that other responsibilities required under the NIH Multiple Project Human Subjects Assurance would be met.

Interim OPRR Actions

In view of NIH's inability to document adequate protections for human subjects involved in at least some of its international collaborative research activities, OPRR began on November 21, 1990, to prepare the requisite documentation for imposing a formal restriction on the NIH Multiple Project Human Subjects Assurance. OPRR also intensified its investigation.

The Acting Director, NIH was notified in writing on January 24, 1991, that OPRR was restricting its approval of the NIH Multiple Project Human Subjects Assurance, effective February 7 (see Attachment B). The restriction excluded from coverage under the NIH Assurance, and thereby required additional protections for, all ongoing, proposed, or future activities involving human subjects as follows:

> (1) Collaborative research with any foreign scientists or institutions by any National Cancer Institute Division of Cancer Etiology intramural scientists.
>
> (2) Collaborative research with any of the following scientists by any NIH intramural scientists: scientists affiliated with the Universite Pierre et Marie Curie (France) or its associated laboratories, clinics, and hospitals (including, but not limited to, Assistance Publique Hopitaux de Paris and Hopital Saint Antoine); scientists affiliated with the Cliniques Universitaries de Kinshasa (Zaire) or its associated laboratories, clinics, and hospitals; scientists affiliated with the Institut National de Recherches Biomedicales (Zaire) or its associated laboratories, clinics, and hospitals.

As a result of this restriction, each project entailing any activities excluded from coverage under the NIH Multiple Project Human Subjects Assurance requires the negotiation of a new OPRR-approved Single Project Assurance from NIH, as well as from the collaborating institution(s), prior to any new involvement, or continued involvement, of human subjects. Single Project Assurances are negotiated individually by OPRR for specific research projects and require prior review and approval by OPRR of the involvement of human subjects in the project's research protocol.

The Acting Director, NIH was also notified in writing that, as of January 24, OPRR's investigation had revealed a general lack of understanding among NIH intramural scientists and the NIH ICRSs concerning their responsibilities relative to the protection of human subjects in international collaborative research (see Attachment B). OPRR therefore recommended that the Acting Director, NIH take the following actions relative to the NIH Multiple Project Human Subjects Assurance:

(1) Designate [the Acting Director, NIH] as the responsible institutional official for all NIH-conducted research involving human subjects covered by the NIH Multiple Project Assurance of Compliance and by any Single Project Assurances to be negotiated.

(2) Direct the evaluation, and modification as needed, of current mechanisms for the review of human subject research to ensure that collaboration by NIH scientists with foreign scientists in research involving human subjects is identified and approved by the appropriate ICRS and that required Assurances of Compliance are negotiated prior to the involvement of human subjects.

(3) Direct the evaluation, and modification as needed, of current mechanisms to ensure that all NIH components recognize and adhere to the authority of the NIH Clinical Center's ICRS structure over all activities involving human subjects.

On January 30, 1991, the Acting Director, NIH notified OPRR that Dr. Edward Rall, the NIH Deputy Director for Intramural Research, had been designated to replace Dr. Rosen as the NIH official responsible for interaction between the NIH Intramural Research Program and the OPRR with respect to Assurances and other aspects of the protection of human research subjects (see Attachment C). This designation was recognized by OPRR on February 1 (see Attachment C, Documents C-I and C-II).

Evaluation by Special Consultants

In order to ensure an impartial and thorough examination of relevant issues, OPRR appointed and assembled a group of consultants from outside NIH to review information and to provide advice concerning (a) the extent that NIH services and/or materials were used in support of the human subjects research under investigation; (b) the nature and degree of NIH scientific collaboration in support of this research; and (c) the adequacy of NIH intramural policies and procedures for the protection of human research subjects, with particular attention to ICRS functions relative to collaborative research (see Attachment D for the complete charge to consultants).

Background materials (including all documents in Attachments B and C, OPRR correspondence with a second complainant, relevant ICRS files, and a partial chronology of events) were forwarded to consultants on January 24 and February 20 (see Attachment D, Document D-I). Consultants assembled in Bethesda on the evening of February 27 and met through March 1. Interviews were conducted with NIH administrators (including Dr. Rall and Dr. Rosen) responsible for the conduct of intramural research and for the protection of human subjects involved in intramural

research; past and present ICRS chairpersons and ICRS staff; and intramural scientists involved in the research under investigation (see Attachment D, Document D-II for agenda).

Each consultant provided OPRR with his or her own individual evaluation of relevant issues based upon the background materials and interviews conducted during the Bethesda meeting, additional documents supplied during and after the Bethesda meeting (see Attachment D, Document D-III), and discussions with each other and OPRR staff. OPRR has carefully considered the evaluations submitted by its advisory consultants (see Attachment E) together with all other relevant evidence. Nevertheless, it is OPRR which has ultimate responsibility and final authority for issuing determinations in this matter relative to the protection of human research subjects.

The findings and recommendations in this report are based on the entire range of information that was obtained in the course of OPRR's investigation. This includes the initial allegations presented by Mr. Crewdson, the NIH report of October 5, 1990, the advice of OPRR's consultants, and information obtained from NIH scientists and French scientists subsequent to the submission of the consultants' reports (see Attachment A). Of particular importance is information that OPRR obtained in face-to-face interviews at NIH with Dr. Daniel Zagury and Dr. Odile Picard on April 25 and April 26, 1991.

OPRR emphasizes that its investigation has been internally guided and directed. A wide variety of sources have been utilized in gathering relevant information. Although Mr. Crewdson is among those who have been queried, he has been generally unresponsive to OPRR requests for information (see Attachment A, particularly July 19 and August 9, 1990).

OPRR Review of Compliance with HHS Human Subjects Regulations in Certain Collaborative AIDS-Related Research Activities

The OPRR investigation focused on the review of compliance with HHS Regulations for the Protection of Human Research Subjects by certain NIH intramural research scientists, primarily scientists from the National Cancer Institute (NCI) Division of Cancer Etiology (DCE) but also including scientists from the NCI Division of Cancer Biology, Diagnosis, and Centers (DCBD) and the National Institute of Allergy and Infectious Diseases (NIAID). Of particular concern was their collaborative AIDS-related research activities involving scientists affiliated with the Universite Pierre et Marie Curie (France), the Cliniques Universitaries de Kinshasa (Zaire), and the Institut National de Recherches Biomedicales (Zaire). OPRR sought to determine which of these collaborative research actions constituted activities subject to the HHS human subjects regulations (45 CFR 46).

OPRR identified nine research "projects" that appeared to be directly relevant to the allegations under investigation. However, these "projects" do not necessarily represent discrete research undertakings. OPRR identified written protocols (one of them incomplete) for only two of the nine "projects," and only three of these "projects" appear to be described in published scientific literature. In addition, written agreements that might fully and exhaustively document the transfer of biological materials to and from NIH intramural scientists were not required during the period under investigation and apparently do not exist.

Projects Involving Human Subjects in Zaire

Beginning in July of 1986, an immunotherapy project (referenced here as Project A) was undertaken in Zaire by scientists affiliated with the Universite Pierre et Marie Curie (France), the Cliniques Universitaries de Kinshasa (Zaire), and the Institut National de Recherches Biomedicales (Zaire). As described by the principal French investigator, Dr. Daniel Zagury, this project initially involved two human subjects with AIDS and was later expanded to include a total of eight such individuals. Results of this project have never been published.

Later in 1986, these same scientists initiated a vaccine program in Zaire. This vaccine program is considered to consist of two projects, although this distinction may be somewhat arbitrary. As described by Dr. Zagury, human subjects in the first vaccine project (Project B) were Dr. Zagury himself; 10 healthy, HIV-seronegative children between the ages of two and nine years; and eight healthy, HIV-seronegative children between the ages of 10 and 18 years. According to Dr. Zagury, these children were permitted to participate in this project on a humanitarian basis at the urgent request of their mothers, who had AIDS themselves. Results pertaining to 12 of these 19 subjects have been reported in the scientific literature (March 1987; April 1988; see Attachment A) without reference to the fact that, with the exception of Dr. Zagury, all subjects were children. Dr. Zagury has stated to OPRR that these children continue to be monitored and remain healthy.

According to Dr. Zagury, the second Zairian vaccine project (Project C) involved approximately 30 HIV-seronegative adults, including military volunteers. This trial was largely unsuccessful. The subjects remained HIV-seronegative, and results of this project have never been published. Dr. Zagury has stated to OPRR that these subjects also remain healthy.

All three of these Zairian projects [i.e., one immunotherapy project (Project A) and two vaccine projects (Project B and Project C)] relied, at least in part, on materials and/or

technical expertise provided by NIH scientists. Most notably, these projects utilized a recombinant vaccinia virus (V25) that was originally supplied to Dr. Zagury by an NIAID intramural scientist (Dr. Bernard Moss) for use in animal research. In December of 1986, an NCI intramural scientist (Dr. Robert Gallo, who is named as a co-author on the [redacted] publication referenced above) informed Dr. Moss about the unauthorized use of the recombinant vaccinia material with human subjects involved in Dr. Zagury's Zairian research program. Upon learning of the use of this material in humans, Dr. Moss refused to supply additional recombinant vaccinia virus to Dr. Zagury. However, Dr. Moss subsequently did provide plasmids and technical instruction necessary for the production of recombinant vaccinia virus which was needed to continue Dr. Zagury's research effort.

OPRR has obtained no definitive information to date regarding the effects of these three projects [i.e., one immunotherapy project (Project A) and two vaccine projects (Project B and Project C)] on the human subjects involved. Dr. Zagury has assured OPRR that the research caused no harm to subjects. However, Dr. Zagury has been unwilling to allow OPRR to review the relevant medical and research records in order to obtain independent corroboration of his statements.

A fourth project (Project D) involved seroepidemiology studies of HIV infection rates in a Zairian military brigade and the brigade's civilian family members and associates. Research activities included serology, Western Blot tests, and viral isolation. Samples of blood from HIV-positive subjects involved in this project, as well as from persons who participated in Project A described above, have been sent to NCI intramural scientist Dr. Robert Gallo for sequencing in order to analyze the extent of genetic drift of AIDS virus envelope proteins in this study population.

A fifth project (Project E) was initiated in late 1987 or early 1988 and involved testing peripheral blood lymphocytes from 14 healthy subjects. These subjects had previously received a recombinant vaccinia virus preparation containing the AIDS viral envelope gene followed by a booster preparation containing a recombinant fragment. According to Dr. Zagury, blood for use in this project was obtained from subjects participating in Project C. Results of this study have been reported in the scientific literature (August 1988; see Attachment A). NCI intramural scientist Dr. Jay Berzofsky is named as principal author of this publication; co-authors include NCI scientist Dr. Robert Gallo, as well as Dr. Daniel Zagury and scientists from the Zairian institutions referenced above.

Projects Involving Human Subjects in France

A sixth project (Project F) was a French immunotherapy study utilizing killed autologous cells infected with recombinant vaccinia virus. This study was approved by the French National Ethics Committee in May 1987 with the recommendation that subjects be limited to patients for whom AZT was contraindicated. As reported in the scientific literature (July 1990; see Attachment A), this study involved two groups of subjects with declining T4 cell counts (14 experimental subjects and 14 matched control subjects). According to the July 1990 publication describing this study, eight subjects in each group continued to take AZT. The July 1990 publication also references five individuals with very low T4 cell counts who received the experimental treatment.

The primary author of this scientific report was a French scientist, Dr. Odile Picard, who was the principal clinical practitioner for this project. Co-authors included NIAID intramural scientist Dr. Bernard Moss (who supplied recombinant vaccinia virus for this project in February 1989), NCI scientist Dr. Robert Gallo, and Dr. Daniel Zagury, who was the principal basic science investigator in France. In May 1990, the St. Antoine Hospital Ethics Committee approved expansion of this project to compare the effects of immunotherapy alone and the effects of immunotherapy with AZT in "discontinuous" treatments.

The French investigators, Dr. Picard and Dr. Zagury, have indicated to OPRR that all subjects in this study were patients for whom AZT was contraindicated, as recommended by the French National Ethics Committee. However, Dr. Picard explained that a number of subjects were afraid to stop taking AZT, so a clinical decision was made to continue them on very low, nontoxic dosages of this drug while they were treated on the research protocol.

Dr. Picard and Dr. Zagury have indicated to OPRR that the five individuals with very low T4 cell counts who are referenced in the July 1990 publication were patients who were enrolled in the trial solely for "compassionate" reasons. These five individuals received exactly the same immunotherapy preparation as other subjects on the research protocol. Up to seven additional patients were subsequently enrolled in this fashion, bringing the total number of subjects involved in this trial to a number approaching 40.

Dr. Picard has explained that "compassionate treatment" in France refers to treatment in accordance with an experimental protocol of terminal patients who are near death and are beyond therapy. According to Dr. Picard, "compassionate treatment" with experimental protocols is permitted in France at the discretion of the physician-researcher after all traditional treatments have been attempted without success. Specific ethics committee review

and approval of "compassionate treatment" cases is not required under French law according to Dr. Picard.

Dr. Picard and Dr. Zagury have acknowledged to OPRR that three of the individuals enrolled in the trial for "compassionate" reasons died following the experimental treatment, although the immediate cause of death may not be precisely known. All three individuals suffered injection-related subcutaneous necrosis that developed after they received local, as opposed to intravenous, injections. Two deaths involved subcutaneous injection, and one involved intramuscular injection. Dr. Picard has stated to OPRR that the experimental treatment shortened the lives of these three patients subsequent to the onset of the injection-related necrosis.

Dr. Picard has indicated that she gave a formal presentation describing these deaths at the annual Laboratory Meeting organized by NIH scientist Dr. Robert Gallo in August 1990. Dr. Gallo, however, has stated that he first became aware of the deaths in January 1991, and at that time did not realize that the deaths involved research subjects. Dr. Picard and Dr. Zagury maintain that the deaths occurred after submission of the 1990 publication. Dr. Picard and Dr. Zagury have prepared an article for publication describing the deaths and their possible causes.

A seventh project (Project G) involved immunization of healthy, HIV-seronegative volunteers with synthetic HIV peptides. It was approved by the French National Ethics Committee in June 1988, with the recommendation that the informed consent document contain a medical certificate declaring that the individual was seronegative before immunization and that any acquired seropositivity should not be considered evidence of infection. The latter information, intended to inform volunteers that they would become seropositive as a result of participation, does not appear in a (signed) consent document that has been obtained by OPRR.

Although NIH scientists have denied direct involvement in this project, Dr. Daniel Zagury, the primary basic science investigator, has acknowledged to OPRR that reagents supplied by NIH scientists have been used for <u>in vitro</u> analyses of the blood samples upon which data from this project are derived. Dr. Zagury has indicated that materials for the vaccine itself were manufactured elsewhere. Dr. Jean-Claude Imbert, the head of the hospital department in which this project was conducted, has publicly characterized this project as involving intellectual collaboration with NCI scientists.

An eighth project (Project H), initiated in early 1989, involved collaboration between NCI scientist Dr. Takis Papas and Dr. Daniel Zagury in the production and purification of specific recombinant vector expressed HIV-1 envelope encoded polypeptides.

According to Dr. Papas, the project included a limited series of in vitro studies involving samples of HIV-1 positive sera.

A ninth project (Project J) is an immunotherapy trial utilizing purified HIV-1 proteins and peptides to be provided by NCI scientists. This proposed collaboration involving Dr. Daniel Zagury has not received NCI administrative approval as of the date of this report.

Compliance with HHS Regulations and the Adequacy of Human Subject Protections

The regulations require that institutions (as opposed to individual scientists) provide a written Assurance of Compliance with HHS human subjects requirements [45 CFR 46.103(a)]. As a result, OPRR views compliance with the regulations in an institutional context. Individual scientists are considered agents of their institution, which has entered into an agreement with OPRR through its Human Subjects Assurance. While the actions of individual NIH scientists precipitated OPRR's investigation, NIH must be held accountable as an institution for the actions of its agents.

As an institution, NIH has contributed substantially to the conduct of the research program of Dr. Daniel Zagury. Individual NIH intramural scientists have maintained a cooperative relationship with Dr. Zagury over an extended period of time. In the course of this relationship, NIH scientists have trained study personnel; performed laboratory analyses; and supplied critical biological reagents for, and reviewed data from, studies involving human subjects. NIH scientists and Dr. Zagury have indicated to OPRR that such activities, including the provision of reagents and the exchange of blood samples, have usually been undertaken freely and informally, most often with no written agreement to define the obligations or responsibilities of the parties involved.

Since 1984, NCI intramural scientist Dr. Robert Gallo has been listed as a co-author with Dr. Zagury on no fewer than 14 scientific publications reporting research that appears to have involved human subjects (see Attachment A). Dr. Zagury has indicated to OPRR that Dr. Gallo supplied him with HIV material as early as 1984, although he notes that Dr. Gallo also supplied the same material to many other scientists working in this field worldwide. Nevertheless, Dr. Zagury credits Dr. Gallo with making entrance into his present field of research possible and with catalyzing a network of colleagues to assist him. Dr. Zagury has further indicated that he considers Dr. Gallo's assistance in interpreting and integrating the meaning of research findings and in preparing manuscripts for publication to have constituted particularly valuable contributions to his

research. Dr. Zagury also appreciates having participated in the annual Laboratory Meeting hosted by Dr. Gallo.

While some may argue that the contributions of individual intramural scientists to certain projects described above did not constitute "collaboration," undisputed settlement of the issue of individual investigator responsibility is not necessary to a determination of institutional responsibility on the part of NIH. NIH is responsible for the protection of human subjects in these projects at a level commensurate with both the individual and the collective involvement of its scientists. The OPRR investigation has revealed a general failure on the part of the NIH Intramural Research Program to provide adequate protection for human research subjects involved in these studies. Failures on the part of those collaborating with NIH scientists have also been identified. These failures are detailed below.

(1) Projects A, B, and C (the Zairian immunotherapy and vaccine studies) relied first upon an apparently unauthorized use in human subjects of recombinant vaccinia materials supplied by NIH, and later upon materials (i.e., plasmids) and technical instruction supplied by NIH after disclosure of the unauthorized use. NIH administrators and supervisors failed to protect human subjects adequately (a) by not requiring written agreements stipulating the conditions under which such materials were transferred, including the prohibition of unauthorized use of such materials with human subjects; (b) by not requiring scientists to submit the subsequent transfer of material and provision of technical instruction for ICRS review after the unauthorized use with human subjects had been disclosed; (c) by not making clear to investigators that co-authorship on scientific publications normally carries with it responsibilities relative to the protection of human subjects involved in the research (responsibilities that are even more serious when children are involved as research subjects); and (d) by not providing sufficient guidelines for NIH review of collaborative arrangements to determine which constituted regulated activities.

(2) Project D (involving analysis of blood samples from HIV-positive subjects) was not submitted for ICRS review. NIH failed to protect human subjects in this project adequately (a) by not making clear to its investigators that such studies required ICRS review, and (b) by not providing a system that ensured the appropriate review of such studies.

(3) Project E (involving tests of peripheral blood lymphocytes) was submitted by NIH investigators for ICRS review, but the following deficiencies in this review resulted in failure to protect human subjects adequately: (a) the NCI-ICRS granted

"retrospective" approval permitting use of data collected prior to ICRS review; (b) the NCI-ICRS granted approval of the project before documentation of its stipulated conditions for approval had been received; (c) once received, the NCI-ICRS accepted inadequate documentation of its stipulated conditions; and (d) the NCI-ICRS failed to notify OPRR of the need for a Human Subjects Assurance of Compliance from the collaborating performance site institution. It appears that the ICRS granted approval for Project E under the false impression that it had been "approved" by OPRR and under the misimpression that, if it had, no further review was required. Confusion within NIH about the respective roles of OPRR and the ICRSs appears to have contributed to this misimpression (as well as to other misunderstandings that have been identified in the course of OPRR's investigation). NIH must be faulted for creating an administrative structure (or vacuum) that has resulted in widespread confusion within NIH about the differing responsibilities of OPRR and the NIH ICRS system.

(4) Project F (the French immunotherapy study) was conducted under an OPRR-approved Single Project Human Subject Assurance (SPA # S-6361-01) from the Universite Pierre et Marie Curie. Modification of the project protocol (a) to include subjects who continued to receive AZT and (b) to include compassionate treatment of subjects with very low T4 cell counts violated the terms of this Assurance which stipulated that "proposed changes in the research activity" must be reviewed and approved by the IRB and reported promptly to OPRR. The failure on the part of the Assurance signatory (Dr. Zagury on behalf of the Universite Pierre et Marie Curie) to notify OPRR promptly of "injuries to human subjects" or "unanticipated problems involving risks to subjects or others" also constituted a violation of the terms of the Assurance. OPRR must be faulted relative to this project (a) for approving an Informed Consent document that was not consistent with the conditions of IRB approval conveyed under the Assurance, (b) for failing to obtain an Assurance from the performance site institution (Hopital Saint Antoine), and (c) for indicating to the NIAID-ICRS that ICRS approval of this project was not required.

(5) NIH scientists have denied direct involvement in Project G (the French vaccine study), and the extent of collaboration is uncertain. Nevertheless, reagents provided by NIH scientists have played a critical role in the analysis of blood samples upon which data from this project are derived. The circumstances surrounding this study indicate that NIH has failed to protect human subjects adequately (a) by not requiring written agreements stipulating the conditions under which reagents were transferred, (b) by not providing a system for appropriate review of such agreements to ensure

adequate human subject protections, (c) by not providing guidelines to its investigators detailing their responsibilities relative to intellectual collaborations in research involving human subjects, and (d) by not providing a system that ensured appropriate review of such collaborations to ensure adequate human subject protections.

(6) Project H included in vitro studies involving samples of HIV-1 positive sera. These studies were not submitted for ICRS review. As in Project D, NIH failed to protect human subjects adequately (a) by not making clear to its investigators that such studies required ICRS review, and (b) by not providing a system that ensured the appropriate review of such studies.

In addition to these specific failures, OPRR found that the intramural scientists interviewed in connection with this investigation were uninformed about their responsibilities relative to the protection of human research subjects under the HHS regulations. These scientists were unaware of the regulatory definition of human subjects and assumed that they had no responsibilities in this area as long as they did not directly inject human beings with experimental materials. Some seemed to believe that compliance with foreign standards was all that was required. Others seemed to be unaware of the applicability of either United States or foreign standards for the protection of human research subjects. There appeared to be virtually no realization that in vitro experiments utilizing human materials may constitute research with human subjects under the HHS regulations, and that such experiments require ICRS review under the NIH Multiple Project Human Subjects Assurance. NIH and its administrators failed to protect human subjects adequately (a) by not providing for sufficient education of these scientists relative to human subject protections, and (b) by not providing sufficient mechanisms to detect and ensure appropriate review of human subjects research conducted by these scientists.

Foreign scientists interviewed by OPRR in connection with this investigation were also uninformed about their responsibilities under HHS regulations relative to the protection of human research subjects. These scientists assumed incorrectly that adherence to the legal and ethical requirements of the countries in which they worked was sufficient for collaboration with NIH scientists or for use of materials supplied by NIH scientists. Dr. Zagury maintained that he had never been clearly instructed about NIH expectations relative to the use of its materials or the protection of human research subjects. He confessed that he did not read thoroughly the requirements of the Single Project Human Subjects Assurance which he signed, and he accepts responsibility for not fulfilling those requirements.

NIH failed to protect human subjects adequately by permitting human subjects research activities (or the exchange of materials) with foreign scientists in the absence of sufficient administrative oversight and education, relative to human subject protections, of those scientists. NIH has a responsibility to ensure that the institutions and scientists with which it conducts or supports human subjects research (or exchanges materials) understand and accept the responsibilities which such relationships with NIH entail. A prerequisite for adequate education of foreign scientists is a thorough understanding of, and adherence to, HHS human subjects regulations and NIH human subjects policies on the part of the NIH scientists with whom they are involved. However, NIH should be able to place a general confidence in institutions that hold an OPRR-approved Human Subjects Assurance of Compliance which covers research activities supported by NIH.

Interviews with ICRS chairs conducted in the course of this investigation revealed an inadequate understanding of ICRS responsibilities relative to documenting (a) that collaborating performance site institutions were in possession of appropriate OPRR-approved Human Subjects Assurances, and (b) that appropriate local IRB approval of collaborative projects had been granted. NIH failed to protect human subjects adequately by not providing clear guidelines and mechanisms through which ICRSs could fulfill these responsibilities.

In summary, OPRR has determined that the NIH system for the protection of human research subjects was inadequate for protecting subjects who became involved in the international research activities reviewed in the course of this investigation. Modifications in existing policies and procedures are necessary to ensure adequate protections for human research subjects involved in international research activities under the NIH Multiple Project Human Subjects Assurance (MPA # M-1000).

Findings:
Current Human Subject Protections

Generally, the OPRR investigation has revealed a disjointed, compartmentalized system of human subject protections within the NIH intramural research community. Lack of centralized and authoritative oversight of research activities covered by HHS human subjects regulations has resulted in uncertainty at all levels of the intramural community regarding individual and institutional responsibilities under the NIH Multiple Project Human Subjects Assurance. The resultant diffusion of responsibility for the protection of human research subjects appears to be fostered by the ill-defined lines of authority, responsibility, and operating procedures that characterize NIH as

an organization made up of semiautonomous Institutes, Centers, and Divisions.

Specific findings address two major areas: (a) NIH's administrative oversight of policies and procedures for the protection of human research subjects, and (b) understanding within the NIH intramural research community of human subject protection policies and regulations.

Specific Findings:
Administrative Oversight

(1) NIH policies and procedures for the protection of human research subjects provide no centralized system of authority that can ensure understanding of and compliance with HHS and NIH human subjects requirements on the part of the NIH Intramural Research Program. Related to this lack of centralized authority is the widespread confusion within NIH about the differing responsibilities of OPRR, NIH administrators and supervisors, and the NIH ICRS system for the protection of human subjects in research conducted or supported by the NIH Intramural Research Program and its scientists.

(2) HHS Regulations for the Protection of Human Research Subjects apply to all human subjects research conducted or supported by the NIH Intramural Research Program and its scientists and clinical investigators, including both domestic and international research undertakings. However, prior to the investigation reported herein, NIH policies have provided no clear, operational definition of human subjects research activities (i.e., of activities that are subject to the HHS human subjects regulations) and no mechanism for decision making in disputed circumstances.

(3) NIH is responsible for the protection of human subjects in research that it conducts or supports at a level commensurate with the collective involvement of its individual components and scientists. However, NIH presently has no policies or procedures to monitor such collective involvement or to ensure that all intramural research involving human subjects receives appropriate review.

(4) The transfer of biological materials and reagents to and from NIH intramural scientists is often accomplished through informal channels. While this practice may be effective for encouraging productive scientific exchange, it prevents NIH from meeting its responsibility to protect human subjects who participate in research that relies upon materials or other resources supplied by NIH.

Specific Findings:
Understanding of Human Subject Protection Policies

(1) Many NIH intramural scientists (and their supervisors), and many scientists with whom they collaborate, are insufficiently informed about HHS Regulations for the Protection of Human Research Subjects, about NIH policies and procedures to ensure protection of human subjects, and about their own specific responsibilities in the area of human subject protection.

(2) NIH intramural scientist Dr. Robert Gallo and collaborating scientist Dr. Daniel Zagury have demonstrated a continuing lack of understanding about HHS human subjects regulations and NIH human subjects policies.

Required Actions:
Current Human Subject Protections

NIH must create a unified system of human subject protections that extends across all relevant NIH Institutes, Centers, and Divisions and has clear authority over the entire intramural community. It must ensure that a central administrative authority is responsible for education of this community and exercises oversight of and control over all human subject protections carried in accordance with HHS regulations and the NIH Multiple Project Human Subjects Assurance.

Within 60 days of receipt of this report, NIH must provide OPRR with a comprehensive plan of action, endorsed by the Director, NIH, for exercising administrative oversight sufficient to bring all NIH activities subject to HHS Regulations for the Protection of Human Research Subjects (45 CFR 46) into full and continuing compliance with the regulations. This plan will constitute a proposed amendment to the NIH Multiple Project Human Subjects Assurance (MPA # M-1000), which governs research involving human subjects conducted or supported by the NIH Intramural Research Program.

The NIH plan must specifically address the findings and recommendations contained in this report and must include the following actions:

(1) NIH must identify a central administrative official with authority to sign, and take responsibility for compliance with, the NIH Multiple Project Human Subjects Assurance. Sufficient staff reporting to this official must be assigned the responsibility of tracking and exercising oversight over all research involving human subjects conducted or supported by the NIH Intramural Research Program.

(2) NIH must establish policies and procedures to assure identification, required initial and continuing review, certification, and required reporting of all human subjects research conducted or supported by the NIH Intramural Research Program. Standard operating procedures to be followed by all intramural personnel must clarify the lines of authority and responsibility for all aspects of the NIH intramural human subject protections system.

(3) NIH must develop and implement an effective program of continuing human subjects education for all appropriate intramural staff (including intramural scientists who are not clinicians and their supervisors). This program must include individual and agency responsibilities under the regulations, as well as an historical perspective and theoretical justification for human subject protections.

(4) Because the duties of NIH Extramural Program personnel sometimes involve human subjects research activities, NIH must develop policies and procedures to bring such activities under an appropriate Human Subjects Assurance of Compliance.

Recommendations: Current Human Subject Protections

The requirements specified in the previous section of this report constitute minimal actions needed to bring the NIH intramural human subject protections system into compliance with HHS regulations (45 CFR 46). OPRR offers the following specific recommendations for NIH to consider in designing its comprehensive plan to implement the required actions.

(1) To ensure effective administrative oversight of all human subjects research conducted or supported by the NIH Intramural Research Program:

(a) NIH should establish an intramural office of human subject protections with administrative and support staff sufficient to implement, coordinate, and document all human subject protection and oversight activities required under the NIH Multiple Project Human Subjects Assurance. The intramural office of human subject protections should reside within the office of a central administrative official (e.g., the NIH Deputy Director for Intramural Research) who shall have authority to sign, and thereby take responsibility for compliance with, the NIH Multiple Project Assurance. The NIH-wide importance of this office warrants that its staff have unencumbered access to the leadership of the Agency.

(b) Within the NIH Multiple Project Human Subjects Assurance, NIH should clearly define the role, responsibility, and accountability of each of the various components of its intramural human subject protection system. The responsibilities of this system should be sharply distinguished from those of OPRR.

(c) NIH policies and procedures for the protection of human research subjects should include clear operational definitions of activities (including purely intellectual collaboration) that are subject to the HHS human subjects regulations and should establish a mechanism to assess prospectively whether proposed activities involve the conduct or support of human subjects research.

(d) NIH policies should define the responsibilities for human subject protection on the part of scientists who accept co-authorship of publications reporting research involving human subjects.

(e) NIH should establish an administrative system of checks to guarantee that all research involving human subjects which is conducted or supported by the NIH Intramural Research Program receives appropriate review within the intramural human subject protection system. Written documentation should be required for research that is exempt from IRB review under the HHS regulations [45 CFR 46.101(b)].

(f) NIH should develop policies and procedures to monitor the collective level (across all relevant NIH Institutes, Centers, and Divisions) of intramural conduct and support of human subjects research involving investigators and institutions outside the NIH.

(g) NIH should require written documentation stipulating the conditions under which all biological materials and reagents intended for use in research involving human subjects are transferred to and from the NIH Intramural Research Program. A system should be established for review of such documentation to ensure adequate human subject protection under HHS regulations and NIH policy.

(2) To ensure understanding within the NIH Intramural Research Program of human subject protection policies and regulations:

(a) NIH should develop mandatory human subjects education programs for all intramural scientists and clinical

investigators. The scope of these programs should be sufficient to ensure an understanding of all relevant regulations and policies for the protection of human research subjects, as well as of the responsibilities incurred by individual investigators engaged in the conduct of research involving human subjects.

(b) NIH should develop policies and procedures to ensure that scientists with whom NIH intramural scientists collaborate are adequately instructed about their responsibilities in the conduct of research involving human subjects. The responsibilities of NIH scientists for ensuring that their collaborators understand NIH expectations relative to the protection of human subjects should also be clearly defined.

(c) NIH should develop special administrative procedures to guarantee compliance with HHS and NIH human subjects requirements in any NIH-supported research activities in which either Dr. Robert Gallo or Dr. Daniel Zagury is involved.

Completion of the Investigation and Final OPRR Action Relative to the NIH Multiple Project Assurance

The findings and required actions contained in this report represent interim actions to ensure the protection of human research subjects under the NIH Multiple Project Human Subjects Assurance (MPA # M-1000). Final OPRR action in this matter will be taken following resolution of the following issues:

(1) NIH bears responsibility for research conducted in Zaire and France that (a) utilized NIH materials or (b) involved the regulated research activities of NIH intramural scientists. OPRR must determine independently and objectively whether human subjects were harmed in any way as the result of their involvement in this research. Up to the time of issuance of this report, however, OPRR's primary source of information regarding current health status of subjects has been the French investigators themselves (i.e., Dr. Daniel Zagury and Dr. Odile Picard). Consequently, OPRR is attempting (through appropriate diplomatic channels) to provide for independent review of medical and research records that may establish the nature and degree of any harm experienced by human subjects in this research.

(2) Current NIH human subject protections are inadequate relative to the conduct of international collaboration that constitutes regulated research. Consequently, OPRR has delineated a number of recommendations and required actions to improve the NIH intramural human subjects protection

system. Restrictions placed on the NIH Multiple Project Human Subjects Assurance effective February 7, 1991, remain in effect until NIH implements improvements in its intramural human subject protections systems (see Attachment B). Such improvements must be reflected in a revision of the NIH Multiple Project Human Subjects Assurance (MPA # M-1000) which will be subject to review and approval by OPRR.

(3) Until these scientists have established a record of strict compliance with HHS Regulations for the Protection of Human Research Subjects, (a) all human subjects research activities involving Dr. Robert Gallo with investigators outside the NIH shall be forwarded to OPRR for additional review and prior approval; (b) no research activities (including shipment of research materials or instruction in research technology) involving Dr. Daniel Zagury shall be permitted by any HHS component or employee without the prior written approval of OPRR.