Advisory Committee on Human Radiation Experiments

95 JUL 21 P4:48

1726 M Street, NW, Suite 600
Washington, DC 20036
202/254-9795
Fax: 202/254-9827

FAX TRANSMISSION COVER SHEET

Date: July 21, 1995

To: Phil Caplan

Fax: 202/456-2215

Re: Letter to Institutions

Sender: Ruth Faden

YOU SHOULD RECEIVE 2 PAGE(S), INCLUDING THIS COVER SHEET. IF YOU DO NOT RECEIVE ALL THE PAGES, PLEASE CALL 202/254-9802.

DRAFT ✦ DRAFT ✦ DRAFT ✦ DRAFT ✦ DRAFT ✦ DRAFT ✦ DRAFT

Date

Dear Institutional Representative,

The Advisory Committee on Human Radiation Experiments has completed its review of 125 contemporary research protocols as part of its Research Proposal and Review Project. Among these proposals was material provided to us by your institution. Some of the documents we examined raised concerns. These concerns emerged in some but by no means all of the proposals we reviewed. They generally fell into these categories:

1. Particularly in research with patient-subjects exposed to more than minimal risk --the inadequate explanation in consent forms of the level of risk encountered by subjects, and overly optimistic discussions of the benefits likely to be realized by the subject through participation in research.

2. The involvement of adults of questionable competence in research that offered subjects no prospect of direct medical benefit and that put them at risk, with inadequate attention to the ethical issues this causes and in particular inadequate attention to questions of capacity to consent and authorization by others.

3. The absence of 'assent' forms in a substantial proportion of protocols involving minors as research subjects, as required.

We report these findings in a general form only, both to inform you of the nature of the Advisory Committee's concerns, and to honor our promise to preserve the confidentiality of the identity of institutions and investigators, as laid out in our letter of request for information on specific protocols sent in October 1994. We would be happy to supply you with more detailed information on the research protocol(s) from your institution reviewed by the Advisory Committee, but please be aware that such a request will require the creation of a publicly available document linking our analysis to specific research protocols and therefore to individual institutions.

We hope you will take this information and review those protocols sent to us, in light of it. Should you desire further information, under the conditions outlined here, please contact the Advisory Committee's associate director, Dr. Jeffrey Kahn, at the address on this letterhead, or by phone at 202/254-9795. Thank you for your continued cooperation in the Advisory Committee's efforts.

Sincerely,

Ruth R. Faden, PhD, MPH
Chair

MEDICAL COLLEGE OF WISCONSIN

95 AUG 15 P2:15
Center for the Study of Bioethics

FAX COVER

CENTER FOR THE STUDY OF BIOETHICS

Date: 8/15

Number of Pages (including this one): 6

To: Phil Caplan

Fax #: 202-456-2215

From: Jeff Kahn

Telephone #: (414) 456-8498

Fax #: (414) 266-8654

MESSAGE:

8701 Watertown Plank Road
P.O. Box 26509
Milwaukee, Wisconsin 53226-0509
(414) 456-8498
FAX: (414) 266-8654

ID: AUG 21'95 11:07

TRANSMIT CONFIRMATION REPORT

NO.	:	001
RECEIVER	:	2025861499
TRANSMITTER	:	
DATE	:	AUG 21'95 11:07
DURATION	:	05'21
MODE	:	STD
PAGES	:	09
RESULT	:	OK

THE WHITE HOUSE
WASHINGTON

OFFICE OF THE STAFF SECRETARY

Fax Transmittal Sheet

TO: Lisa Schiavo

Fax Number: 586-1499 **Phone Number:**

FROM: Phil Caplen

SUBJECT:

DATE:

NUMBER OF PAGES (including cover sheet): 9

MESSAGE:

Let me know what you think.

Thanks

If all pages are not received, please call 202/456-2702

[letter to institutions participating in the project]
Date

Name
Address
Address

Dear Institutional Representative,

The Advisory Committee on Human Radiation Experiments has completed its review of documents concerning 125 contemporary research protocols, as part of its Research Proposal Review Project. Among these proposals was material provided us by your institution.

The Advisory Committee's review of research proposal documents was not intended to audit particular institutions or individual protocols. Rather, by examining documents from a wide variety of research funded by many agencies of the federal government, we hoped to offer insight into the general state of the protection of the rights and interests of human subjects.

In the course of this review, we identified several issues that raise concern and deserve further attention and which will be noted in our final report. These include:

1. Language problems in the consent forms of some proposals that place patient-subjects at greater than minimal risk. These problems include an inadequate explanation of the trade-offs involved in chosing between participating in such research and standard medical care, overly optimistic portrayals of the likely benefits to be realized, and inadequate explanation of the impact of research procedures on quality of life and personal finances.

2. Research that appeared to offer no prospect of medical benefit to subjects with questionable capacity to consent and involved greater than minimal risk.

3. The absence of 'assent' forms in some proposals involving minors as research subjects.

About 18 (14%) of the proposals we reviewed raised one or more of these issues.

We wish to emphasize the limitations of our evaluation of the research proposals we reviewed, which was based solely on selected documents. It is possible that some of the proposals that raised concerns for us based on these documents, would, upon a more complete review, be deemed unproblemmatic from a human subjects perspective. Conversely, it is possible that some of the proposals whose documents raised no concerns may nevertheless have inadequacies affecting the rights and interests of human subjects which we could not detect. We hope you will take this information and review those protocols sent to us in light of it.

As we noted in our initial letter requesting documents from your institution, as a Federal Advisory Committee, we are obligated under the Federal Advisory Committee Act (FACA)

to allow public access to materials once we receive or create them. As a consequence, we are required to make available the results of the Research Proposal Review Project to the public or government funding agencies upon request, including the Advisory Committee's analysis of documents from particular proposals. Should a Freedom of Information Act (FOIA) request from a member of the public be made to us for documents concerning a research project at your institution, we will seek your assistance regarding any information that is exempt under FOIA (e.g., certain trade secrets or confidential business information) before complying with this request. For requests independent of FOIA, such as those from government funding agencies to which your institution is a contractor, we plan to notify you of any requests for Committee materials related to your institution, and will copy you on all responses to these and other requests. Should your institution desire information about particular research proposals that were part of the Advisory Committee's review, we would be happy to provide it. Please make such a request in writing.

If you have any questions about this aspect of the Committee's work, please contact the Advisory Committee's associate director, Dr. Jeffrey Kahn, at the address on this letterhead, or by phone at 202-254-9795.

I would like to take this opportunity to thank you on behalf of the Advisory Committee for your willingness to cooperate in our efforts to maintain and improve the ethics of human subject research. Your willingness to voluntarily make available documents for review indicates your institution's commitment to research ethics, which we very much appreciate. We have been gratified by the openness shown by the biomedical research community, as indicated by your institution's response to our request. It is important evidence of improvement in the ethics of human subject research over the fifty year history reviewed by the Committee.

Sincerely,

Ruth R. Faden, PhD, MPH
Chair

[letter to accompany responses to AGENCY requests for Project results/info]

Ellyn Weiss
DOE

Dear Ellyn,

As part of the Advisory Committee's commitment to openness, and under the terms of the Federal Advisory Committee Act, the attached materials are being provided as you have requested. I would like to emphasize that they represent raw and unanalyzed data, and have little meaning separate from the full results of the Advisory Committee's "Research Proposal Review Project." The Advisory Committee on Human Radiation Experiments neither offers nor endorses any analysis of, or conclusions regarding the attached material. The Advisory Committee's conclusions regarding the project from which this material comes can be found in its final report.

The methodology by which the Advisory Committee undertook its Research Proposal Review Project was intended to yield general insights into the state of protections for subjects in contemporary biomedical research, and not for the purpose of auditing institutions or individual research protocols.

We wish to emphasize the limitations of our evaluation of the research proposals we reviewed, which was based solely on selected documents. It is possible that some of the proposals that raised concerns for us based on these documents, would, upon a more complete review, be deemed unproblemmatic from a human subjects perspective. Conversely, it is possible that some of the proposals whose documents raised no concerns may nevertheless have inadequacies affecting the rights and interests of human subjects which we could not detect.

In light of the above, the limitations of this review must be understood:

--Paper records may be incomplete or inaccurately portray research practices, such that a research proposal raising serious ethical concerns on paper may in actuality be ethically acceptable, and vice versa.

--Review of paper records alone cannot take account of researcher-subject, or researcher-IRB interactions.

--The Advisory Committee's sample was not intended to be representative of all contemporary biomedical research, but rather to sample from the types of research within the scope of the Committee's efforts.

--No claim of quantitative social science research is made or should be implied from the results, findings or conclusions of the Research Proposal Review Project.

--The project's coding forms should not be viewed as data, but more accurately represent reviewers' sketchy notes for discussion of particular research proposals.

--The scoring scale for proposals is intentionally subjective and should be viewed only as a rough way to distinguish proposals that appear exemplary based on available documents (those scoring a '1') from those raising concerns (those scoring a '3', '4', or '5').

I trust that whatever follow-up the Department of Energy undertakes with respect to individual institutions will bear the above in mind. Please contact me should you have any questions or comments about this material.

Sincerely,

Ruth R. Faden, PhD, MPH
Chair

enclosures

[cover memo to accompany responses to public requests for RPRP info]

As part of the Advisory Committee's commitment to openness, and under the terms of the Federal Advisory Committee Act, the attached materials are being made publicly available upon request. They represent raw and unanalyzed data, and have little meaning separate from the full results of the Advisory Committee's "Research Proposal Review Project." The Advisory Committee on Human Radiation Experiments neither offers nor endorses any analysis of, or conclusions regarding the attached material. The Advisory Committee's conclusions regarding the project from which this material comes can be found in its final report.

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--The scoring scale for proposals is subjective and should be viewed only as a rough way to distinguish exemplary proposals (those scoring a '1') from those raising concerns (those scoring a '3', '4', or '5').

Questions about these limitations or the enclosed materials should be directed to the Advisory Committee's associate director, Dr. Jeffrey Kahn, at the address on this letterhead, or by phone at 202-254-9795.

ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS
1726 M STREET, N.W., SUITE 600
WASHINGTON, D.C. 20036

December 9, 1994

[redacted]

The Advisory Committee on Human Radiation Experiments (ACHRE) was created by President Clinton to evaluate the ethical and scientific criteria applicable to human radiation experiments carried out or sponsored by the U.S. Government. In addition to examining the history of government-sponsored human subject research involving radiation, ACHRE also is charged with examining current policies and practices related to human radiation research and making recommendations for revised federal policy as appropriate. In order to carry out this portion of its charge, ACHRE has undertaken a Research Proposal Review Project. ACHRE needs your assistance in this vital undertaking.

The Research Proposal Review Project aims to evaluate the extent to which the rights and interests of persons currently involved as subjects of radiation research conducted or supported by the U.S. Government appear to be adequately protected, and to compare this level of protection with that afforded the subjects of non-radiation research. ACHRE will review research proposals and supporting materials from two groups of studies: a sample of human subject research proposals involving ionizing radiation that were approved and funded by federal agencies between fiscal years 1990 and 1993, and a parallel comparison sample of studies not involving ionizing radiation funded by the same agencies during the same time period. For proposals in both of these groups, ACHRE will evaluate whether the informed consent procedures, selection of

subjects, and balancing and distribution of risks and benefits appear to be appropriate.

This project is crucial to ACHRE's ability to make meaningful recommendations based on contemporary data. We plan to review two categories of documents for the research proposals described above: The research proposal itself, which we have obtained from the funding agency; and the relevant documents, described more fully below, from the Institutional Review Board (IRB) that reviewed the proposal.

From lists of intramural and extramural research proposals approved and funded in recent years from the Departments of Health and Human Services (DHHS), Defense (DOD), Energy (DOE), Veterans Affairs (VA), and NASA, we have drawn a sample of 54 extramural research proposals involving ionizing radiation and 27 non-radiation studies from 41 different institutions. The study that was selected from your institution is listed on the attached sheet. We would greatly appreciate your providing us with the following materials for this proposal:

(1) Full application submitted to the [redacted] IRB by the study investigator(s);

(2) Consent form, as submitted with the application to the IRB;

(3) Consent form, as approved by the IRB;

(4) Official approval letter from the IRB;

(5) Documentation concerning any changes to the research design, methods, or consent form that have been approved by the IRB after the IRB's initial approval of the study;

(6) If applicable, the application submitted to the Radioactive Drug Research Committee (RDRC);

(7) If applicable, the official letter of approval from the Radioactive Drug Research Committee (RDRC); and

(8) If applicable, the application submitted to and the official letter of approval from any institutional human use committee other than the IRB or RDRC.

We understand that you may have concerns regarding the confidentiality of this information, and about the linkage of study results with particular institutions or research proposals. Our approach to these concerns is as follows:

First, we understand that some institutions may have concerns about the protection of

portions of these materials. The grant proposals, which we have obtained directly from the relevant federal agencies, are already available from these agencies to members of the public who make a request under the Freedom of Information Act (FOIA). As a Federal Advisory Committee, we generally are obligated under the Federal Advisory Committee Act (FACA) to allow public access to these and any additional materials once we receive them. Should a FOIA request be made to us for documents concerning a research project at your institution, we will seek your assistance regarding any information that is exempt under FOIA (e.g., certain trade secrets or confidential business information) before complying with this request.

The identities of the 41 institutions from whom documents are being requested, as well as the identities of the institutions who comply with the request, will become part of the public record. However, when we report the results of our review, none of our findings will linked to any institution, investigator, or named research proposal. Should our review suggest evidence of a potential violation of federal regulations, it is our plan to inform the research institution so that it can comply with its obligation to pursue potential misconduct and report such research to federal oversight agencies, as appropriate.

I hope you will agree to assist us in this most important project. The interests of the research community are best served by an publicly accessible review of its practices involving the protection of research subjects. Public confidence in research can only be strengthened by the cooperation of the research community in such efforts.

We would like the requested materials as soon as you can provide them, but no later than December 30, 1994. They should be sent to ACHRE at the address on this letterhead, to the attention of Sara Chandros. ACHRE has a very short timeline for completion of this project and development of its final recommendations so your prompt response would be greatly appreciated. Please do not hesitate to call me or Dr. Jeffrey Kahn, the staff's Associate Director, at (202) 254-9795 should you have any questions or concerns not addressed here. I greatly appreciate your assistance in this matter.

Sincerely,

Ruth R. Faden, Ph.D., M.P.H.
Chair

cc. [redacted]

Attachment 1

ACHRE Proposal # [redacted]

Title of Study: [redacted]

PI: [redacted]

Institutional Project # [redacted]

ACHRE would appreciate your providing us with the documents pertaining to this study as listed in the following checklist. Please return this form along with the documents.

Please check the appropriate box:

Enclosed	Not Applicable	
☐	☐	Full application submitted to your IRB by the study investigator(s)
☐	☐	Consent form, as submitted with the application to the IRB
☐	☐	Consent form, as approved by the IRB
☐	☐	Official approval letter from the IRB
☐	☐	Documentation concerning any changes to the research design, methods, or consent form that have been approved by the IRB and after the IRB's initial approval of the study
☐	☐	Application submitted to the Radioactive Drug Research Committee (RDRC)
☐	☐	Official letter of approval from the Radioactive Drug Research Committee (RDRC)
☐	☐	The application submitted to and the official letter of approval from any institutional human use committee other than the IRB or RDRC *Please specify the name of the committee:* _____

DRAFT ✦ DRAFT ✦ DRAFT ✦ DRAFT ✦ DRAFT ✦ DRAFT ✦ DRAFT

Date

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2. The involvement of adults of questionable competence in research that offered subjects no prospect of direct medical benefit and that put them at risk, with inadequate attention to the ethical issues this causes and in particular inadequate attention to questions of capacity to consent and authorization by others.

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We hope you will take this information and review those protocols sent to us in light of it. Should you desire further information, please contact the Advisory Committee's associate director, Dr. Jeffrey Kahn, at the address on this letterhead, or by phone at 202/254-9795. Thank you for your continued cooperation in the Advisory Committee's efforts.

Sincerely,

Ruth R. Faden, PhD, MPH
Chair

ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENT
1726 M Steet, N.W., Suite 600
Washington, D.C. 20036
(202) 254-9795 (Phone)
(202) 254-9827 (Fax)

95 JUL 24 P4:32

FAX TRANSMITTAL

NUMBER OF PAGES (including cover): 6

TO: Phil Caplan 202-456-2215

FROM: Ruth Faden / Jeff Kahn (via Sara Chandros)

DATE: July 24, 1995

RE: Letters to institutional representatives

If there are any problems with the transmission of this fax, please call (202) 254-9795.

MESSAGE:

Per your conversation with Ruth, attached are (1) the original letter sent to institutions requesting documents, and (2) the most recent draft of the follow-up letter. Please call me if you have any questions at 202-254-9852 (direct)

– Sara Chandros

COVER SHEET

FAX

To: Phil Caplan
Fax #: (202) 456-2215
Subject: Letter from D.A. Henderson to R. Faden
Date: August 9, 1995
Pages: 6, including this cover sheet.

COMMENTS:

I understand from Wendy Baldwin that you have not seen a copy of this letter. If you need any other information, let us know.

From the desk of...

Lily O. Engstrom
Assistant Director
Office of Extramural Research, NIH
Shannon Building, Room 150
Bethesda, Maryland 20892

(301) 402-2245
Fax: (301) 402-3469

FAX TRANSMISSION

From: D.A. Henderson, M.D., M.P.H.
The Johns Hopkins University

To: Lilly Engstrom **FAX No:** 301-402-3469

Date:

Number of pages to follow this page:

If all pages not received, or transmission is not clear, call or fax the numbers below.

Message:

A copy of my letter to Ruth.

DA.

OFFICE

624 North Broadway
Baltimore, MD 21205
FAX No: (410) 550-6898
Phone No: (410) 955-1624

HOME

3802 Greenway
Baltimore, MD 21218
FAX No: (410) 889-6514
Phone No: (410) 889-2880

July 31, 1995

Dear Ruth,

Who would have believed that in the comparatively short span of time allotted, the Committee and its staff could possibly navigate such a complex set of issues, let alone retrieve and digest the volume of material you have and eventually produce an erudite, thoughtful report? I salute all of you for an incredible effort! While I am not in full accord with all findings and recommendations, I can understand alternative conclusions and recommendations and appreciate that reasonable persons will sometimes differ.

There is, however, one critical problem area about which I am deeply concerned. This problem area is the RPRP whose presentation and summary I would strongly advise be subjected to critical reconsideration. I found this to be a seriously flawed chapter in almost every respect and jarringly at variance with a report which is shaping up as a balanced, scholarly review and thoughtful consideration of an important subject. I'm sorry I had not seen the draft of this chapter until this past week but now, having seen it, I hasten to write.

The RPRP, as I understood it and as page one of Chapter 15 states, was intended as an exercise "to gain <u>some understanding</u>" of current practices in human subjects research through a review of documents available to local IRBs so as "to <u>simulate</u> a review parallel to theirs". The statement of purpose goes further in pointing out that "the purpose of the RPRP <u>was not to audit the performance of individual researchers and institutions, nor the specific IRBs</u>". Indeed, in the discussion section (pages 42-43), there is a reasonable elaboration as to the many limitations in the methodology and possible interpretations of the study itself and implicitly an explanation as to why an audit as such was simply not possible.

Somewhere along the line, however, the intent of the review and the recognition of its intrinsic limitations seem to have been forgotten and the Committee plunged ahead to perform what I can only identify as an audit! Not only is there an audit but efforts are even made to quantify what are all too obviously, highly subjective qualitative judgements made by individual members of a Committee especially selected to represent a wide range of scientific expertise. It would seem unlikely, to say the least, to expect

comparable assessments across the board from such a diverse group. Finally, when all the numbers are summed, the percentages derived and the results graphed, there is the strong implication that the findings are representative of the research universe today.

Let us first consider the nature of the sample. The RPRP sample, as noted, was intended to assure that some studies were included from each funding agency and from each biomedical category of radiation research. Notably, no effort was made to draw a random sample proportionate in size and composition to the "N" in each of the different boxes, nor was there any reason to do so under the original intent of the study. However, if one wants to make responsible statements about the overall behaviour or performance of the research enterprise as a whole (e.g., 40% of all research proposals had ethical problems) much, much more explicit attention would have to be given to the sampling methodology as well as considerable statistical manipulation to take into account the very different-sized Ns in the different boxes. However, given the very small numbers examined such an adjustment would almost certainly not be possible in any case. Note for HHS that 43 pprogram protocols were examined in a year when there were 16,972 projects and sub-projects involving human subjects research. In brief, neither sample size nor the methodology permits conclusory judgements about the nature of the whole of the research establishment.

Equally distressing to me was the Committee's subsequent effort to label all proposals on an arbitrary 1 to 5 scale of ethical acceptability. Given the number of people vetting the research proposals, I would have to assume that there must have been very explicit definitions as to precisely how one would categorize a proposal, for example, as a 2 rather than a 3, and appropriate training sessions to assure some reasonable comparability in judgement by different raters. I was puzzled to find no definitions in the text. However, as I read on, I began to sense that perhaps there were no explicit definitions but rather an assigned rating based on a "Gestalt" response. My reason for believing this was quite simply the enumeration of the many factors which caused reviewers to rate proposals somewhat higher or lower. Page 10 tended to endorse this conclusion in stating that ratings of 4 and 5 were "found to be highly problematic" and so were being lumped together for analysis. By the time one reached the top of page 12,

the rating of 3 had joined 4 and 5 as a "poor rating" and was then analyzed with 4 and 5! Later, it is implied that a rating of 2 had to be viewed with suspicion.

The text then describes the many factors which troubled the reviewers, at the same time weaving through this discussion many caveats about methodology. I found myself wondering, for example, as to how an otherwise exemplary proposal would be rated if the reviewer could not comprehend the science, perhaps because of a lack of his own expertise. Or whether my Phase I measles vaccine trial might be rated a 5 rather than a 1 because the consent form suggested that the subject might be subsequently protected against measles.

I was surprised, in fact, by the extraordinary emphasis given to the premise that "Phase I studies should never be presented as treatment". I found this to be an astonishing statement. A great deal of experimental work precedes a Phase I study and unless such work suggests that the drug or vaccine is likely to have a specific effect, one doesn't proceed with a Phase I trial! Can one not suggest to the patient that there is hope the drug might have an effect but that it remains to be proven? The text, as written, says "no" but then note on page 17 a Phase I study which is cited and commended by the Committee for a consent form which refers to "new forms of therapy"!

I note that reviewers criticized a $100 cash payment (page 18), forgetting perhaps that the Committee's own patient subjects were each being paid a sum of money which was not intended to cover either travel expense or loss of income.

The consent forms come in for strong criticism and certainly this is a difficult area. But who is to decide what is an adequate consent form? Where is the line to be drawn between too much information which overwhelms the subject and too little information which is insufficiently informative? Where is the line between a satisfactory, technically accurate presentation and an unsatisfactory one which omits or simplifies in an effort to validly inform? As we all know, determining what is a satisfactory consent form is a highly subjective matter about which honorable people can and often will strongly disagree. Moreover, a local IRB often will factor into this equation the nature of personal interchange intended and indeed the nature and track record of the research

team itself. How adequately can a Committee person and a staff member rate a proposal with no further information than that available on a few written sheets of paper?

Finally, I note that "for 29 of the 125 proposals, reviewers could not even begin to evaluate the scientific merit of the proposals". In part, as the text states, they lacked the scientific expertise and, in part, they felt the scientific documentation to be inadequate. Can it be said, therefore, that nearly 25% of all proposals are scientifically unintelligible? I think not. As we know, IRBs normally consist of many persons with diverse expertise and thus are better able to interpret protocols than would be one Committee evaluator. Moreover, when there is uncertainty about items in a proposal, investigators often are requested to elaborate in writing or to appear before the IRB. How many proposals were downgraded because of this factor on the rating scale?

Ruth, I am wholly confident that there have been and are now problems specifically of the type enumerated and that we need to take steps to improve the system. There is no reason why these cannot be cited as problems noted on review of a sample of proposals. Likewise, recommendations can follow from such a purely descriptive account of this effort.

Presenting all of this as a quantitatively sound, methodologically reasonable exercise is only to invite valid criticism which could well color acceptance of the broader report. Thus, I can only advise in the strongest terms that you reconsider this chapter as it now stands. The credibility of a distinguished Commission is at stake.

All best regards,

ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENT
1726 M Steet, N.W., Suite 600
Washington, D.C. 20036
(202) 254-9795 (Phone)
(202) 254-9827 (Fax)

95 AUG 22 P5 : 10

FAX TRANSMITTAL

NUMBER OF PAGES (including cover): 8

TO: Phil Caplan

FROM: Jeff Kahn

DATE: 8/22

RE: _____

If there are any problems with the transmission of this fax, please call (202) 254-9795.

MESSAGE:

[letter to institutions participating in the project]
Date

Name
Address
Address

Dear Institutional Representative,

The Advisory Committee on Human Radiation Experiments has completed its review of documents concerning 125 contemporary research protocols, as part of its Research Proposal Review Project. Among these proposals was material provided us by your institution.

The Advisory Committee's review of research proposal documents was not intended to audit particular institutions or individual protocols. Rather, by examining documents from a wide variety of research projects funded by many agencies of the federal government, we hoped to offer insight into the general state of the protection of the rights and interests of human subjects. Our objective was not to make judgments about the ethics of particular research projects. Instead, our goal was to determine whether, based on a review of documents, there is reason to be concerned about aspects of the involvement of human subjects in research.

In the course of this review, we identified several issues that raise concern and deserve further attention and which will be noted in our final report. These include:

1. Apparent deficiencies in the consent forms of some proposals that place patient-subjects at greater than minimal risk. These deficiencies include an inadequate explanation of the trade-offs involved in choosing between participating in such research and standard medical care, overly optimistic portrayals of the likely benefits to be realized, and inadequate explanation of the impact of research procedures on quality of life and personal finances.

2. Complexity and high level of the language used in consent forms.

3. The absence of 'assent' forms in some proposals involving minors as research subjects.

4. The recruitment and involvement of subjects with questionable capacity to consent in research projects that appeared to offer no prospect of direct medical benefit to them and yet involved greater than minimal risk.

About 18 (14%) of the proposals we reviewed raised one or more of these issues. These studies were scored as '4' or '5' on a five-point evaluative scale developed by the Advisory Committee for this project, with a higher score representing greater concern over the ethics of the proposal as presented in the available documents. These scores and assessments of various elements of the research projects are recorded on a coding form for each proposal. [The

proposal sent to us by your institution was among this group, and as the enclosed materials indicate, received a score of '4' ['5'].] [The proposal sent to us by your institutions was not among this group, but as the enclosed materials indicate, received a score of '3'. This score indicates that the documents about this proposal raised some concerns although less serious concerns than a proposal scoring '4' or '5').]

[The proposal sent to us by your institutions was not among this group, and received a score of '1' ['2']. This score indicates that the proposal raises no more than minor concerns.]

We wish to emphasize the limitations of our evaluation of the research projects we reviewed, which was based solely on selected documents. From the outset, the Committee neither desired nor thought it possible (because of our limited tenure and limited resources) to make judgments about the extent to which 125 research projects were *in fact* ethically acceptable. This would have required a careful evaluation of far more than the documents that we received.

It is possible that some of the research projects that raised concerns for us based on the documents reviewed, would, with the provision of additional information, be deemed unproblematic from a human subjects perspective. Conversely, it is possible that some of the research projects whose documents raised no concerns may nevertheless have inadequacies affecting the rights and interests of human subjects that we could not detect.

As promised in our initial letter to you, when the Committee reports the results of our review, none of our findings will be linked to any institution, investigator, or named research proposal. However, as we noted in our initial letter requesting documents from your institution, as a Federal Advisory Committee, we are obligated under the Federal Advisory Committee Act (FACA) to allow public access to materials once we receive or create them. As a consequence, we are required to make available the results of the Research Proposal Review Project to the public or government funding agencies upon request, including the Advisory Committee's analysis of documents from particular proposals.

[THIS PARAGRAPH NOT IN LETTER TO 1/2s] If you would like to respond to the concerns raised by the documents provided by your institution, we would be happy to receive such a response and make it a part of the Committee's official records on your institution's proposal. Your response will not be used in the Advisory Committee's deliberations, which focused not on individual projects but on general concerns about possible deficiencies in the ethics of human subjects research. However, your response will reside with the archival materials related to the proposal from your institution and the Research Proposal Review Project. This augmented material would then accompany any response to requests for materials related to your institution's proposal. Our timeframe until the issuance of the Committee's final report is very short, and we strongly recommend that you send us your response before the Committee's materials are placed in the National Archives. To accomplish this, we must receive materials in our offices by September 15, 1995. After this

date, materials can be deposited with the National Archives directly. I apologize in advance for the short deadline.

Should a Freedom of Information Act (FOIA) request from a member of the public be made to us for documents concerning a research project at your institution, your assistance regarding any information that is exempt under FOIA (e.g., certain trade secrets or confidential business information) will be sought before complying with this request. For requests independent of FOIA, such as those from government funding agencies to which your institution is a contractor, we plan to notify you of any requests for Committee materials related to your institution, and will send you copies of all responses to these and other requests. [THE FOLLOWING ONLY FOR 1/2s: Should your institution desire information about particular research proposals that were part of the Advisory Committee's review, we would be happy to provide it. Please make such a request in writing. For your information, institutions whose proposals scored '3', '4', or '5' are being offered the opportunity to augment the materials we reviewed for this project. Since proposals scoring '1' or '2', such as that from your institution, raised no or only minor ethical concerns, it would be less useful to those in the future to provide additional materials about your proposal to the project archives.]

If you have any questions about this matter, please contact the Advisory Committee's associate director, Dr. Jeffrey Kahn, at the address on this letterhead, or by phone at 202-254-9795.

I would like to take this opportunity to thank you on behalf of the Advisory Committee for your willingness to cooperate in our efforts to maintain and improve the ethics of human subject research. Your willingness to voluntarily make available documents for review indicates your institution's commitment to research ethics, which we very much appreciate. We have been gratified by the openness shown by the biomedical research community, as indicated by your institution's response to our request. It is important evidence of improvement in the ethics of human subject research over the fifty year history reviewed by the Committee.

Sincerely,

Ruth R. Faden, PhD, MPH
Chair

enclosures

[letter to accompany responses to AGENCY requests for Project results/info]

Ellyn Weiss
DOE

Dear Ellyn,

As part of the Advisory Committee's commitment to openness, and under the terms of the Federal Advisory Committee Act, the attached materials are being provided as you have requested. I would like to emphasize that they represent raw data, and have little meaning separate from the full results of the Advisory Committee's "Research Proposal Review Project." The Advisory Committee on Human Radiation Experiments neither offers nor endorses any analysis of, or conclusions regarding the attached material.

The methodology by which the Advisory Committee undertook its Research Proposal Review Project was intended to yield general insights into the state of protections for subjects in contemporary biomedical research, and not to evaluate or audit institutions or individual research protocols.

We wish to emphasize the limitations of our evaluation of the research projects we reviewed, which was based solely on selected documents. It is possible that some of the research projects that raised concerns for us based on these documents, would, with the provision of additional information, be deemed unproblematic from a human subjects perspective. Conversely, it is possible that some of the research projects whose documents raised no concerns may nevertheless have inadequacies affecting the rights and interests of human subjects that we could not detect.

In light of the above, the limitations of this review must be understood:

--Paper records may be incomplete or inaccurately portray research practices, such that a research proposal raising serious ethical concerns on paper may in actuality be ethically acceptable, and vice versa.

--Review of paper records alone cannot provide information about researcher-subject, or researcher-IRB interactions.

--The Advisory Committee's sample was not intended to be representative of all contemporary biomedical research, but rather to sample from the types of research within the scope of the Committee's efforts.

--No claim of generalizability to all biomedical research is made or should be implied from the results, findings or conclusions of the Research Proposal Review Project. The Project's results

represent a small sample aimed at gaining general insights into the process for protecting the right and interests of research subjects.

--The project's coding forms should be viewed as a summary of lengthy discussions between pairs of reviewers after individually considering the elements of the protocol in depth.

--The scoring scale for proposals should be viewed only as a rough way to distinguish proposals that appear exemplary based on available documents (those scoring a '1') from those raising concerns (those scoring a '3', '4', or '5').

I trust that whatever follow-up the Department of Energy undertakes with respect to individual institutions will bear the above in mind. Please contact me should you have any questions or comments about this material.

Sincerely,

Ruth R. Faden, PhD, MPH
Chair

enclosures

[cover memo to accompany responses to public requests for RPRP info]

As part of the Advisory Committee's commitment to openness, and under the terms of the Federal Advisory Committee Act, the attached materials are being made publicly available upon request. They represent raw data, and have little meaning separate from the full results of the Advisory Committee's "Research Proposal Review Project." The Advisory Committee on Human Radiation Experiments neither offers nor endorses any analysis of, or conclusions regarding the attached material.

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Questions about these limitations or the enclosed materials should be directed to the

Advisory Committee's associate director, Dr. Jeffrey Kahn, at the address on this letterhead, or by phone at 202-254-9795.