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BERKELEY: DONNER LABORATORY AND DONNER PAVILION

May 8, 1975

James L. Born
James McRae
Henry Stauffer

Re: New LBL Procedures for Protection of Human Subjects

Attached for review are drafts of various documents pertaining to the implementation of "Protection of Human Subjects" at LBL:

1. LBL Administrative Memo
2. Memo to Associate Directors
3. Procedures -- with multiple attachments
4. Form
5. Questions regarding policy and detail

Your comments and suggested changes are sought. Once these have been incorporated, I propose to send this material to George Pappas for eventual discussion with Lorraine McGraw.

Baird Whaley

BW:df
encls.

HUMAN SUBJECTS
LBL 11 1976

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UNIVERSITY OF CALIFORNIA—(Letterhead for interdepartmental use)

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LBL Administrative Memo

Re: Protection of Human Subjects

LBL has revised its procedures for reviewing projects involving human subjects, to comply with new Department of Health, Education and Welfare (DHEW) regulations (which have been adopted by ERDA)?. Henceforth, any such project will require review and approval by the Berkeley Campus Committee for Protection of Human Subjects (CPHS), prior to initiation.

Two members of the LBL staff -- Drs. James McRae and Henry Stauffer of the Biology and Medicine Division -- will serve on the CPHS and will also act as a screening committee for LBL projects. In addition, any LBL project involving the exposure of patients or normal subjects to radiation for diagnosis, therapy, or investigation, will require approval of an LBL Human Use Committee prior to consideration by the CPHS.

The DHEW regulations are very comprehensive. It is important to note that <u>all</u> projects involving subjects or patients must be submitted for prior review, since the CPHS is required to determine both the existence of "risk" (as defined by DHEW), and, if risk is present, its acceptability. In addition to the obvious medical programs, the regulations specifically cover all research activities utilizing human fluids and tissues, including those in which these substances are provided by LBL to, or are received for analysis at LBL from another institution. Also covered are projects in which the investigator is the only subject.

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After initial approval continuing projects must be reviewed at least annually. Research activities involving human subjects which are on-going as of this date will gradually be submitted to the CPHS for review in the near future.

It is the intent of both LBL and the CPHS to follow a rule of reason with respect to the amount of documentation required for "no-risk" or very low risk procedures. However, LBL is under obligation to insure that all projects are submitted for prior review, however minimal or innocuous the involvement of human subjects may appear to be.

Implementing procedures will be furnished separately to programatic Associate Directors.

GLP

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Note to Associate Directors

Re: New procedures for "Protection of Human Subjects"

In response to new DHEW regulations for the protection of human subjects, LBL has revised its procedures as outlined in the accompanying material. Additional copies are available from the Administration Office.

It is important that these procedures be made known to key staff members, and all investigators who are, or who conceivably could become involved with research utilizing human subjects. TheDHEW regulations are very comprehensive, and extend to many types of activities which may not, on the surface, appear to be included. While most covered projects will be in the Biology and Medicine Division, there may be some projects, now or in the future, in other Divisions.

In addition to insuring that all proposed new projects involving human subjects are submitted for review and approval by the Campus Committee for the Protection of Human Subjects, it is necessary for LBL to identify and submit to CPHS all such activities which are now taking place. Toward that end, I request that each Associate Director survey his program and submit to _____ a brief description of each on-going project in which human subjects are utilized. We will then schedule the gradual submission of protocols to the CPHS in the near future.

A.M. Sessler

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LAWRENCE BERKELEY LABORATORY

PROCEDURES FOR REVIEW OF INVESTIGATIONS INVOLVING HUMAN SUBJECTS

PROTOCOLS AND CONSENT FORMS

Each investigator planning a project which involves human subjects must prepare a protocol and a consent form. The protocol must be signed by the Investigator and the Divisional Associate Director. Guidelines for Human Subject protocols are appended as attachment I. Attachments II and III are examples of recently approved protocols.

Consent forms should closely follow the format of Attachment IV, which has been approved by the General Counsel's office. Attachment V sets forth some helpful information for consent forms (prepared by) the Berkeley campus Committee for the Protection of Human Subjects (CPHS). Attachments VI and VII are examples of recently approved consent forms.

Collaborative Projects — The following is no longer acceptable (B) 5/30/75

In the context of these procedures, collaborative projects are those in which one or more of the following activities are shared between LBL and another instituion: clinical management of a patient; diagnostic, therapeutic, or investigative procedures; obtaining body fluids or tissues, (including those from normal subjects); and analysis of fluids, tissue or clinical data. Activities in which staff members of other institutions participate, but in which the involvement of human subjects is entirely under the control of LBL, are not considered collaborative for the purposes of this procedure.

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DHEW regulations and CPHS procedures require written indication of approval from an appropriate source at the collaborating institution. The responsibility for securing this approval rests with the investigator and the necessary documents should be submitted with the protocol. Detailed requirements have not yet been established by CPHS; investigators will be informed when CPHS announces its requirements. In the meantime, questions regarding collaborative projects may be directed to the CPHS office, M-11 Wheeler Hall, Campus extension 2-7461.

Investigational New Drugs

Special requirements pertain to protocols which involve investigational new drugs (IND). These requirements are outlined on the Certification/Declaration form (HEW 596 Rev 10-74) which is appended as Attachment VIII. When such substances are obtained from another organization, that organization must hold IND approval from the Food and Drug Administration (FDA) and the required information must be included in the protocol. If the substance is to be prepared at LBL, the Laboratory must secure its own IND approval. In the latter situation, investigators must allow sufficient time to first prepare and submit the IND, and preferrably sufficient additional time to negotiate with the FDA should it raise objections.

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Special Requirements for Extramural Applications

Human subject protocols for projects supported entirely from ERDA fnnds need not be submitted until the detailed research plan is complete. However, applications to some funding agencies, notably NIH, require CPHS review, with certification to accompany the application, for research proposals in which the involvement of human subjects is probable, but the precise way in which they will be utilized is indefinite. This would occur when human subject involvement depends on the uncertain outcome of instrument development, animal or phantom studies, synthesis of compounds, etc. A protocol must be submitted, setting forth the general nature of expected human subject participation, a statement that detailed protocols will be submitted when plans are definite, and an assurance that the activity will not be started until CPHS approval is received. Attachment IX is an example of such a protocol, recently approved by CPHS. ~~Not yet approved~~ approved 5/19/75

and others??
NIH requires that the protocol and consent form be incorporated as an integral part of the research proposal, with original signatures of the Principal Investigator and the Responsible Administrator. Since the original of the application goes forward to the agency, and does not pass through the CPHS, the "original" protocol for CPHS must also bear original (not xeroxed) signatures of these individuals.

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Finally, DHEW regulations ~~CPHS procedures~~ require review by ~~their~~ CPHS ~~secretariat~~ of all proposals submitted to (which agenceis?), which are declared by the investigator not to involve human subjects, to confirm that assertion. This is a safeguard for an investigator who, through imperfect understanding of the complex BHEW rules, reaches the honest, but mistaken, conclusion that his ~~their~~ proposal does not involve human subjects, when in fact it does. Failure to discover and rectify such an error may lead to outright rejection of the application by the agency. The Associate Director for Administration will arrange for review of such applications.

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TIMING AND SUBMISSION OF DOCUMENTS

Investigators should submit to the CPHS, M-11 Wheeler Hall, Berkeley campus, the original and ___ copies of the protocol, consent form, and documents relating to collaboration. The original protocol should bear the original (not xeroxed) signatures of the investigator and the programatic Associate Director. Protocols associated with extramural applications should be accompanied by ___ copies of the application. This material should also be accompanied by the original and the first copy of form RL-XYZ, "Notification of Research Project Involving Human Subjects". The remaining copies should be distributed, with attachments, as indicated on the form.

CPHS will forward the necessary documents to the Screening Committee for LBL proposals, and, when necessary, to the LBL Human Use Committee. Findings of these groups will be transmitted back to the CPHS for consideration, although ~~they are free to~~ committee members may contact the investigator directly to secure additional information, or to suggest changes.

The CPHS meets once per month, usually during the second or third week. Required material should reach the CPHS office not later than _____. Complex protocols, those with more than low risk, and those involving exposure to radiation (which must be considered by the LBL Human Use Committee) should be submitted _____ in advance of the CPHS meeting, at which they are to be considered.

Investigators should bear in mind that present DHEW regulations require review of NIH proposals (and???) before the application deadline date, with certification of approval to accompany the application.

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In no event may the work proceed prior to receipt of CPHS approval. CPHS approval/disapproval shall be provided in writing to the Investigator, with copies to the Associate Director for Administration and the Programatic Associate Director.

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Attachment F

HUMAN USE COMMITTEE GUIDELINES FOR THE PREPARATION OF PROTOCOLS

Each protocol submitted for review must contain information in sufficient detail and be written with sufficient clarity for the Committ to be able to render an informed judgement. Protocols must be signed by the principal investigator or project director. It is the responsibilit of the secretariat to forward protocols for Committee action. Inadequat protocols will be returned and hence may result in unnecessary delays in submitting proposals. Protocols for research to be done in cooperation with another institution must be approved by the respective Human Use Committees of both.

As a minimum, protocols should consist of the following elements:

1. Describe the proposed research, its significance, and explain its possible benefits to the subject(s) and to society in general, using language that is intelligible to educated laypersons.

2. Tell what has already been done in animals or phantoms and state why studies with human subjects are now necessary or desirable.

3. Specify how the subject population will be selected and, if applicab give an explanation for using special population groups, such as minors, prisoners, the mentally disabled or others whose ability to give voluntary, informed consent may be in question.

4. State if the projected work involves research on the nature and effe of marijuana and halucinatory drugs, drug abuse, or investigational new drugs, including new radiopharmaceuticals.

5. Mention where in the Laboratory or cooperating institution and precisely how the human subjects are to be studied, and include in this description the number of subjects, an estimate of the duration of the investigation, and an indication of the methods of analysis to be employed.

6. Examine the potential harm to the subjects from physical agents, such as noxious chemicals or ionizing radiations (where applicable, compu the whole body dose and that to the organ(s) at risk), and outline the measures to be taken to safeguard the subjects against such effe

7. Consider the possible psychological, emotional or socially deleterio effects upon the subjects, and describe the means to be taken to minimize these (including confidentiality safeguards) and give an assessment of their probable effectiveness.

8. Analyze the risk/benefit ratio, if that is not obvious from the foregoing.

9. Include with each protocol submitted to the Committee a consent for The consent form should be written in language readily understandab to the subject, should explain exactly what is to be done and why, should compare any risks that may not be clear to the subject to ri with which he/she is more likely to be familiar (e.g. "the radiatio dose is less than that of a chest x-ray").

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HUMAN SUBJECT PROTOCOL-I Example. Attachment II

1. Benefits: Human blood plasma will be used in the present studies in order to isolate the lipid-containing particles or lipoproteins. Certain of the lipoproteins have been indicated as predisposing individuals to arteriosclerosis and coronary heart disease. Since coronary diseases cause more than 50% of the deaths in our population, research on physical properties, chemical composition and metabolism of human plasma lipoproteins is indicated in order to obtain insights on how to control such diseases.

2. How subjects will be used: Not more than one unit of blood (500 cc) will be drawn from donors by venipuncture by licensed clinical technologists under medical supervision of Donner Laboratory. Alameda County Blood Bank criteria will be used in determining frequency of donor use; thus, blood will be drawn at intervals of not less than 8 weeks and no more than 5 times a year for any given donor. Before drawing blood, hematocrits will be determined with a lower limit of 41 for males and 39 for females. If 25 ml or less blood is withdrawn, no hematocrit will be determined before blood withdrawal. A Consent Form will be executed for each withdrawal. Plasma will be isolated from the subject's whole blood and the plasma fraction will be subjected to ultracentrifugation to isolate various lipoprotein components. Studies will be carried out on the electrophoretic distribution, chemical composition, and electron microscopic structure of the isolated lipoproteins.

3. Description of subjects: Volunteer adult subjects, both male and female, will be used. Subjects will include normal individuals as well as patients with identified hyperlipemias, coronary disease, renal dysfunction or thyroid disease. Some female subjects on birth control pills will also be studied.

4. Risks and discomforts: There will be no deleterious effects to the subjects other than the minor discomfort of the venipuncture and the risk encountered in a normal blood donation program. Although the majority of people experience no difficulty when donating blood, a few feel faint or weak during or following the blood donation. This research does not involve "violations of normal expectations" since all material will be used solely for our research on lipoprotein,physical and chemical properties, and metabolism.

5. No deleterious effects or violations are anticipated.

6. Written consent will be obtained. A copy of Consent Form is attached.

7. Should any lipoprotein abnormalities or low hematocrits be uncovered in presumed normal subjects during the course of our investigations, we would make such findings known to the subject's physician.

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Example Attachment III

Human Subject Protocol

The use of human subjects in the coming year will be confined to a study of erythropoietic marrow distribution, comparing radioactive iron (^{52}Fe) with Indium-chloride (^{111}In). It is important in diagnosis to have an accurate assessment of total erythropoietic marrow and its distribution. Our research requires that we make this determination using two different tracers. Iron is a physiological tracer but is not readily available and is less easily imaged than indium-chloride. It has already been established that in most instances the distribution of indium-chloride and radioactive iron are similar. However, there appear to be a limited number of patients in whom there is a discrepancy. By studying patients with different hematological disorders, both with iron and indium-chloride it is hoped to determine in which disease states indium-chloride does not give a true picture of erythropoietic marrow. All subjects will have the benefit of an accurate portrayal of their erythropoietic marrow with radioactive iron which will be valuable in their immediate management and prognosis. The additional indium-chloride scan will not help in their diagnosis.

The radioactive iron marrow distribution study provides information about marrow function and has become a standard laboratory diagnostic procedure in the Donner Laboratory Clinic. The upper limit of radiation dose to the bone marrow of a normal adult has been calculated to be 2.5 rads for a 100 μCi dose (Human Bone Marrow Distribution Shown *in vivo* of ^{52}Fe and the Positron Scintillation Camera. Anger, H.O. and Van Dyke, D.C., Science 144:1587-1589, 1964).

Indium-chloride has been approved by the FDA for advanced clinical trials in patients for the purpose of determining the sites

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and extent of marrow function. Indium-chloride is being used according to the protocol of Medi-Physics, Inc. The patients will receive no more than 2 mCi for adults weighing 70 kg or more and proportionately less for lighter people. Subjects under 18 years of age will not be studied unless there are exceptional indications. The radiation dose has been calculated to be 2.4 rads to the bone marrow, 4.5 rads to the liver, 0.5 rads to the total body, including the gonads, and 0.3 rads to the uterus, for each mCi of tracer administered.

Both isotope imaging techniques involve intravenous injection of a radioactive tracer and imaging 24 to 48 hours later. Imaging takes about 2 hours.

Subjects will be patients referred to the Donner Clinic and all age groups will be included. A complete hematological work-up including bone marrow cytology and ^{59}Fe tracer kinetics will be performed as part of the normal medical management of the patients. Both bone marrow imaging techniques involve similar risks to the patient as other nuclear medicine procedures and radiological tests.

The records and information obtained will be transmitted to the referring physician for use in the patient's immediate management. Medical privacy will be maintained. A copy of the consent form is attached.

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Attachment IV

UNIVERSITY OF CALIFORNIA

CONSENT TO ACT AS HUMAN SUBJECT

(REGULAR FORM)

Subject's name _____

Date: _____

1. I hereby authorize _____
[name of person(s) who will perform the

_____ and/or such assistants as may
procedure(s) and/or investigation(s)]

be selected by him to perform on _____
(Insert "me" if subject can sign on his own behalf, or the subject's name if the subject is a minor or is otherwise unable to sign)

the following procedure(s) and/or investigation(s):

(Describe in detail, in language which will provide a fair explanation of the procedure(s) and their purposes, including an identification of those procedures which are experimental.)

2. The procedure(s) and/or investigation(s) listed in Paragraph 1

has (have) been explained to me by _____
(Name)

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3. I understand that the procedure(s) and/or investigation(s) described in Paragraph 1 involves (involve) the following possible risks and discomforts:

(Describe in detail)

and that the possible benefits of the procedure(s) and/or investigation(s) are as follows:

(Describe in detail)

4. (To be used when the procedure(s) is (are) intended to be of a possible therapeutic benefit to the patient-subject)

I have been advised of the following appropriate alternative procedures that would be beneficial to _____:
(see 1. above)

(Describe in detail any such alternative procedures)

5. I understand that _____
[Name of person(s) who will perform procedure(s)
_____ and/or such assistants as may be selected by
and/or investigation(s)]
him will answer any inquiries I may have at any time concerning the procedure(s) and/or investigation(s).

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6. I understand that I may terminate participation in the study at any time without prejudice to future care or to any possible reimbursement of expenses, compensation, employment status, or other entitlement, except as provided herein, and that, owing to the scientific nature of the study, the investigator may in his absolute discretion terminate the procedure(s) and/or investigation(s) at any time. In the event that compensation for participation is to be paid, and participation is terminated by the subject or by the investigator, I understand that the subject will be entitled to payment of a sum based upon the scientific value to the study of the information obtained from the participation, provided, however, that in no event shall the subject receive less than _____ per cent of the agreed compensation if he/she continues to participate beyond the _____ (Describe the applicable time period) _____ of the study.

SUBJECT'S SIGNATURE _____

WITNESS _____

(If subject is a minor, or otherwise unable to sign, complete the following):

Subject is a minor (age ____), or is unable to sign because

_____

_____

_____ Father

_____ Guardian

_____ Mother

[redacted]

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Attachment II

[redacted]. It should be noted that the "standard" consent forms provided in the Chancellor's Memorandum of November 8, 1972 ("Policy and Procedures Governing the Protection of Human Subjects") were intended to serve as models of the basic kind of information that should be included in a consent form, but that they may be stylistically and substantively inappropriate for your particular project. Thus, while every consent form must contain the first five basic elements of "informed consent" that are described in the standard, approved forms, each consent form should be appropriate to the project under consideration. Element 6 [redacted] of the standard, approved consent forms [redacted] not necessary in every project, although in certain cases the researcher may judge them to be desirable.

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Example Attachment VI

CONSENT TO ACT AS SUBJECT FOR
RESEARCH AND INVESTIGATIONS - I

Subject's name_____ Date_____

1. I hereby authorize_____
   Name of person(s) who will perform procedure(s) or investigation(s)

   and/or such assistants as may be selected by him to perform the following procedure(s) and investigation(s):

   Withdrawal of not more than 500 cc of blood for serum lipoprotein investigations. I understand that at least eight weeks must elapse after a 500 cc donation before additional blood may be withdrawn, and that I may not have 500 cc withdrawn more frequently than five times per year.

2. The procedure(s) and investigation(s) listed in Paragraph 1 has(have) been explained to me by_____
   Name

3. I understand that the procedure(s) and investigation(s) described in Paragraph 1 involve the following possible risks and discomforts: the minor discomfort of venipuncture; and the risk encountered in a normal blood donation program. (Although the majority of people experience no difficulty when donating blood, a few feel faint or weak during or following the blood donation.) The potential benefits of the investigation are as follows: Advancement of knowledge on the control of cardiovascular disease; with respect to patients, help in detection of possible lipoprotein abnormalities.

4. Should any lipoprotein abnormalities or low hematocrits be uncovered during the course of this investigation, I agree to having this information made known to my physician._____
   Name of physician

5. I understand that I may terminate my participation in the study at any time.

   Subject's signature_____

   Witness_____

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Example Attachment VII

CONSENT TO ACT AS SUBJECT FOR
RESEARCH AND INVESTIGATIONS UNDER
USPH GRANT CA 08370

Your physician suspects that you have a problem involving your bones and bone marrow.

Patient's Name_____Date_____

1. I hereby authorize_____
   Name of person(s) who will perform procedures and investigations,
   and/or such assistants as may be selected by him to perform the following procedures and investigations:

   a. Inject radioactive iron today and take whole body scans the following day. The radioactive iron shows the places in the body where blood is manufactured.

   b. Inject radioactive indium, which is being investigated as a tracer (i.e., material that gives off a signal) to show the sites of blood formation. Take whole body scans, or pictures of the signals given off by the indium, 2 days later to compare with the scans taken with the radioactive iron. The indium scan is not essential for your diagnosis. Indium is cheaper and more readily available and is used in many centers in place of radioactive iron to look at the places in the body where blood is manufactured. In most patients iron and indium give the same answers. Our research has shown that in some blood disorders there are significant differences and that indium may not give an accurate picture. It is our aim to discover the types of blood disorders in which indium may be used.

2. The procedures and investigations listed above have been explained to me by _____.

3. I understand that the procedures and investigations described above involve the following possible risks and discomforts:

   a. The radioactive iron scan is necessary for the investigation of my suspected blood disease and involves some radiation to my bone marrow. The indium scan adds some further radiation dose, but the total radiation dose from both procedures is comparable to that received in special medical investigations using X-rays or radioisotopes.

   b. The radioactive tracers have been approved for experimental clinical trial by the Federal Drug Bureau.

   c. Discomforts: Both radioactive tracer tests involve the injection of a drug into a vein in the arm. Imaging procedures involve lying on a comfortable bed for extended periods (1-2 hours).

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d. Benefits: These studies will result in information leading to a better understanding of my disease. The two tests sometimes give different information and our research is aimed at determining the type of blood disorder in which this happens and what it means.

5. I understand that _____ will answer any inquiries I may have at any time concerning the procedures and investigations. I understand that I may terminate participation in the study at any time without prejudice to my medical care.

SUBJECT'S SIGNATURE: _____

WITNESS: _____

(If subject is a minor, or otherwise unable to sign, complete the following):

Subject is a minor (age: ____), or is unable to sign because

_____

_____

_____ _____

Father Guardian

_____

Mother

1089490

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PROTECTION OF HUMAN SUBJECTS
CERTIFICATION/DECLARATION

☐ GRANT ☐ CONTRACT ☐ FELLOW ☐ OTHER
☐ NEW ☐ RENEWAL ☐ CONTINUATION
IDENTIFICATION NUMBER (if known) _____

Attachment VIII

STATEMENT OF POLICY: *Safeguarding the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW is primarily the responsibility of the institution which receives or is accountable to DHEW for the funds awarded for the support of the activity. In order to provide for the adequate discharge of this institutional responsibility, it is the policy of DHEW that no activity involving human subjects to be supported by DHEW grants or contracts shall be undertaken unless the Institutional Review Board has reviewed and approved such activity, and the institution has submitted to DHEW a certification of such review and approval, in accordance with the requirements of Public Law 93-348, as implemented by Part 46 of Title 45 of the Code of Federal Regulations, as amended, (45 CFR 46).*

1. TITLE OF PROPOSAL OR ACTIVITY

2. PRINCIPAL INVESTIGATOR/ACTIVITY DIRECTOR/FELLOW

3. DECLARATION THAT HUMAN SUBJECTS EITHER WOULD OR WOULD NOT BE INVOLVED

☐ A. No individuals who might be considered human subjects, including those from whom organs, tissues, fluids, or other materials would be derived, or who could be identified by personal data, would be involved in the proposed activity. (If no human subjects would be involved, check this box and proceed to item 7.)

☐ B. Human subjects would be involved in the proposed activity. Subjects would include; ☐ NONE of the following, ☐ minors, ☐ fetuses, ☐ abortuses, ☐ pregnant women, ☐ prisoners, ☐ mentally retarded, ☐ mentally disabled. Under section 6. Cooperating Institutions, on reverse of this form, give name of institution and name and address of official(s) authorizing access to any subjects in facilities not under direct control of the applicant or offering institution.

4. DECLARATION OF ASSURANCE STATUS/CERTIFICATION OF REVIEW

☐ A. This institution does not have an active assurance on file with DHEW that covers or applies to this application. When requested by DHEW this institution will submit an assurance and implementation procedures to comply with the requirements of the *Federal Regulations on Protection of Human Subjects (45 CFR 46).*

☐ B. This institution has an approved general assurance (DHEW Assurance Number _____), or an active special assurance for this ongoing activity, on file with DHEW. The signer CERTIFIES that all activities in this application proposing to involve human subjects have been reviewed and approved by this institution's Institutional Review Board in a convened meeting on the date of _____ in accordance with the requirements of the *Code of Federal Regulations on Protection of Human Subjects (45 CFR 46).* This certification includes, when applicable, requirements for certifying FDA status for each investigational new drug to be used (see reverse side of this form).

The Institutional Review Board has determined, and the institutional official signing below concurs, that:

either ☐ human subjects will not be at risk;

or ☐ human subjects will be at risk.

5. and 6. SEE REVERSE SIDE

7. SIGNATURE OF INSTITUTIONAL OFFICIAL _____ date _____

TITLE _____ telephone no. _____

8. NAME AND ADDRESS OF INSTITUTION

HEW 596 (Rev. 10-74)

ENCLOSE THIS FORM WITH THE PROPOSAL OR RETURN IT TO REQUESTING AGENCY.

new revision 2/75

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5. INVESTIGATIONAL NEW DRUGS - ADDITIONAL CERTIFICATION REQUIREMENT

Section 46.17 of Title 45 of the *Code of Federal Regulations* states, *"Where an organization is required to prepare or to submit a certification . . . and the proposal involves an investigational new drug within the meaning of The Food, Drug, and Cosmetic Act, the drug shall be identified in the certification together with a statement that the 30-day delay required by 21 CFR 130.3(a)(2) has elapsed and the Food and Drug Administration has not, prior to expiration of such 30-day interval, requested that the sponsor continue to withhold or to restrict use of the drug in human subjects; or that the Food and Drug Administration has waived the 30-day delay requirement; provided, however, that in those cases in which the 30-day delay interval has neither expired nor been waived, a statement shall be forwarded to DHEW upon such expiration or upon receipt of a waiver. No certification shall be considered acceptable until such statement has been received."*

INVESTIGATIONAL NEW DRUG CERTIFICATION

To certify compliance with FDA requirements for proposed use of investigational new drugs in addition to certification of Institutional Review Board approval, the following report format should be used for each IND: (attach additional IND certifications as necessary).

- IND FORMS FILED: ☐ FDA 1571, ☐ FDA 1572, ☐ FDA 1573
- Name of IND and sponsor _____
- Date of 30-day expiration or FDA waiver (future date requires followup report to DHEW) _____
- FDA restriction _____
- Signature of investigator _____ date _____

6. COOPERATING INSTITUTIONS - ADDITIONAL REPORTING REQUIREMENT

Section 46.16 of Title 45 of the *Code of Federal Regulations* imposes special requirements on the conduct of studies or activities in which the grantee or prime contractor obtains access to all or some of the subjects through cooperating institutions not under its control. In order that the DHEW be fully informed, the following report is requested when applicable.

Use following report format for each institution other than grantee or contracting institution with responsibility for human subjects participating in this activity: (attach additional report sheets as necessary).

- Official of cooperating institution authorizing access to subjects.
  Name of official _____
  Title _____ telephone _____
- Name and address of institution _____
- Subjects: status (wards, residents, students, employees, patients, etc.) _____
  number _____ age range _____

NOTES:

HEW 596 (Rev 10-74) (Back)

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Attachment IX

BERKELEY: DONNER LABORATORY AND DONNER PAVILION

Example

April 28, 1975

Lorraine McGraw
Committee for the Protection
of Human Subjects
M-11 Wheeler Hall
University of California
Berkeley campus

Re: NIH 1 P07 RR 01005-01
"SEM-Secondary Ion Mass Spec - A Bio-Tech Resource", T.L. Hayes, Ph.D.

I am enclosing a copy of my NIH proposal, "SEM-Secondary Ion Mass Spec. - A Bio-Tech Resource", which was submitted through LBL for the February 1, 1975 deadline. Support is requested beginning January 1, 1976. This proposal consists of two distinct but interrelated activities: The development and construction (with ETEC Corp.) of a Scanning Electron Miscroscope with secondary ion analysis capability; and the employment of this instrument in visualizing and analyzing various biological samples, some of which are expected to be of human origin, by various investigators, many of whom will be collaborators from other institutions.

The development of the instrument will be a phased activity in which the Scanning Electron Microscope (SEM) and the Secondary Ion Mass Spectrometer (SIMS) will initially operate separately. This will be followed by a preliminary period of combined operation during which various design modifications may be made depending on performance characteristics. Certain biomedical applications will be undertaken during these two phases. When the instrument has reached its optimal performance level a wide variety of biomedical applications will be made. Since the proposal contemplates the completed instrument as a nation-wide resource, the biomedical experiments will involve collaborating investigators from a number of other institutions. A tentative list of investigators and their probable projects is included as Table I (page 15) in the proposal, but others, with as yet unforseen projects, are expected to be added in the future. The initial involvement of tissues and fluids is therefore dependent on both the progress of instrument development, and the interest and availability of investigators with projects suitable to the instrument's operation capabilities at a given point in time. It is not possible now to pinpoint these activities with the specificity required for the preparation of particular protocols.

We can, however, assure the Committee that all human tissues will be residual, being obtained as a result of normal treatment by licensed physicians, and will be obtained in such a way that anonymity will be preserved. Such assurances as may be required by the CPHS will be secured from the cooperating institutions, and no such activities will be undertaken prior to your approval of specific protocols. The same will be true of human fluids with the possible exception that a very small amount of normal blood may be drawn at Donner. This would be analagous to the protocol already approved by the CPHS in relation to the NIH application of Lindgren, and would be submitted for your ratification with respect to my proposal before being undertaken.

S/ James L. Born

Thomas L. Hayes, Ph.D.

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BERKELEY: DONNER LABORATORY AND DONNER PAVILION

May 7, 1975

Re: NIH 1 P07 RR 01005-01
"SEM-Secondary Ion
Mass Spec.-A Bio-Tech
Resource" - T.L. Hayes,
Ph.D.

Adendum to Human Subjects Protocol

The protocol of April 28, 1975 indicates that tissues and fluids of human origin will be residual from standard and accepted diagnostic and therapeutic measures employed by licensed physicians in the clinical management of patients. The quantities would be those required by the employment of these standard measures.

However, we do not wish at this point to rule out the possibility that under certain circumstances, tissues and fluids would be obtained in amounts beyond that required for standard clinical procedures, or possibly without relation to them. Should activities of this sort appear in the future to be desirable, we will submit to the CPHS detailed protocols for review, and we will, of course, not proceed prior to CPHS approval.

S/

James L. Born, M.D.
Responsible Administrator

Thomas L. Hayes

T. L. Hayes, Ph.D.
Principal Investigator

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DRAFT

LAWRENCE BERKELEY LABORATORY

NOTICE OF PROPOSED PROJECT INVOLVING HUMAN SUBJECTS

To: Committee for Protection of Human Subjects
M-11 Wheeler Hall
Berkeley Campus

_____
Date

Title of Protocol _____

Title of Research Project _____

Investigator Name _____

Divisional Associate Director Name _____

LBL Account Number _____

Funding: ☐ ERDA
☐ Other (Specify) _____
Agency Deadline _____

Does this protocol involve the exposure of ☐ patients ☐ normal subjects to Radiation ☐ yes ☐ no

Does this protocol involve investigative new drugs ☐ yes ☐ no If yes, specify

whether the IND is issued to ☐ LBL ☐ Other _____
Name of Organization

Date of Expiration of 30 day interval/FDA Waiver _____

Does this Protocol involve collaboration with another institution ☐ Yes ☐ No

If Yes, _____
Name of Organization(s)

(Attached required documentation)

For CPHS use

Refer to LBL Screening Committee _____
Date

Refer to LBL Human Use Committee _____
Date

(Anything else CPHS wants)

Distribution:
Original - CPHS (Retains)
Copy #1. - CPHS (Transmit to LBL Screening/Human Use Committees)
Copy #2. - LBL Assoc. Dir. for Administration (Retains)
Copy #3. - LBL Programmatic Assoc. Dir.
Copy #4. - Investigator

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There remain unanswered questions, some relating to basic policy, and others to matters of detail.

Policy Questions

1. Protocols associated with extramural applications must be accompanied by copies of the proposal. What, if anything, shall accompany protocols related to ERDA projects? The 189 form? Some of these are not very detailed, and others might not be specific with relation to new projects conceived during the year.

2. Bearing in mind that ERDA has adopted DHEW ~~MX~~ procedures, and that DHEW now requires a declaration of non-involvement for DHEW applications of human subjects, does this imply that CPHS must review all of LBL's 189 forms?

3. Will it be necessary to review ERDA-supported human subject projects in the Spring, immediately prior to 189 form submission? And if so, will it be necessary, in accord with DHEW rules, for proposals in which the involvement of human subjects is certain, but not ~~MX~~ definitive, to prepare general, preliminary protocols. Hopefully the answer to both questions is "no"! the contrary would bury us all in an unmanageable morass of paper at a time of year when we are least able to cope with it.

4. Protection of Human Subjects is an LBL-wide responsibility. The present (Donner) Human Use Committee (Born, Budinger, McRae, Stauffer, Jones) is composed exclusively of

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Biology and Medicine Staff members. Should this membership be augmented or some of the present members replaced? Who will decide and when? Should not an LBL Committee be formally appointed by Dr. Sessler?

5. Is LBL, as an ERDA prime contractor, exempt in any way from FDA IND requirements for radioactive pharmaceuticals? If so, under what circumstances, and does this extend to ~~XXX~~ projects supported by other agencies?

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Questions of Detail

1. The proposed form "Notification of Research Project Involving Human Subjects" (which may be regarded by some as bureaucratic excess) is intended to inform those concerned of current Human Subjects activities, particularly pending protocols. I assume that the LBL administration office will wish this information, especially with reference to extramural applications. Some Programatic Associate Directors may not wish to keep records; certainly we will want to do so in Bio-Med. The alternate to a form is a cover memo, with copies. The form has the advantage that all of the requisite points of information can be pre-printed; investigators may forget to include essential information in a memo, generating time-consuming exchanges of correspondence or telephone calls.

2. The proposal to route protocols directly from investigators to CPHS, and then back to the LBL Screening or Human Use Committee, has already been questioned. The rationale for doing so is to place as much of the clerical workload as possible at the point where the LBL-provided clerical assitance is located. It is based on the assumption that we will finance an addition to the CPHS staff. The alternate would involve internal routing within LBL, perhaps through the Administration Office, to the Screening and/or Human Use Committees, possibly back to the investigator if there were deficiencies or questions, with forwarding to CPHS of only finished products. This would place an additional workload at several points within LBL, with no means provided to cope with it, since there appears no practical way to utilize the services of the LBL-paid clerical, who will presumably reside in M-11 Wheeler.

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The proposed routing will place LBL investigators in the same relation to CPHS as those on the campus, save for having to complete and distribute the "Notification ..." form.

3. Different numbers of copies of various documents will be required for different types of protocols. For example: A complex protocol for therapy at the Bevalac, associated with an NIH application, will be referred to the LBL Human UseCommittee. If Committee membership remains at 5, each member will undoubtedly need a copy of the proposal in addition to the copy for CPHS. A simple protocol for drawing small amounts of normal blood for biochemical analysis will be referred no further than the LBL Screening Committee, requiring at most two additional copies of the proposal.

Shall we address these varying requirements in the "Procedures", or do we contemplate that additional copies will be requested when needed by CPHS? We should bear in mind that it is generally easier to make additional copies during one reproduction run, and that the unexpected necessity of separately duplicating additional copies of a bulky proposal can ~~constitute a~~ cause a considerable burden or delay.

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Rev Lowrance 5/29 "1/yes" 90 days FR 5/22/75

4. Has a "grace period" been instituted? If so, the "Procedures" must be modified to incorporate it.

5. Does the Administration Office wish to have a copy of the protocol material, with or without a copy of the proposal, appended to its copy of the "Notice..." form? The Divisional Associate Director? ("Yes" for Bio-Med).

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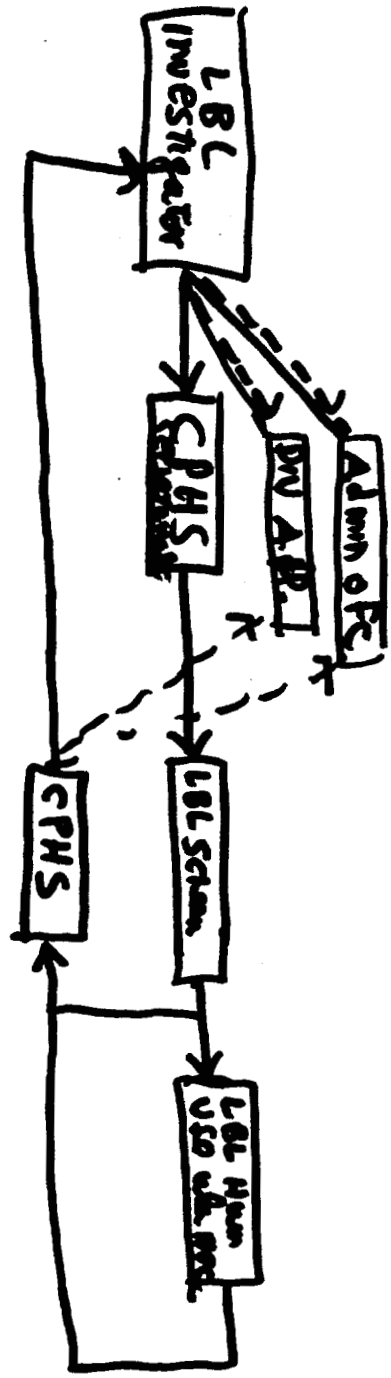

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DRAFT

February 24, 1976

LBL Administrative Memo

Re: Protection of Human Subjects

LBL is formalizing its procedures for reviewing projects involving human subjects in accordance with Department of Health, Education and Welfare (DHEW) regulations and the LBL Assurance to DHEW. Safeguarding the rights and welfare of human subjects is the responsibility of the institution, and these regulations extend to all projects regardless of funding source. Procedures will entail prior review and formal approval of any project involving human subjects ~~where a~~ ~~is considered to be~~ "at risk" - defined as exposure to the possibility of harm, whether physical, psychological, sociological or other. In addition to the obvious medical programs, the regulations specifically cover all research activities utilizing human fluids and tissues, including those in which these substances are provided by LBL or are received from another instituion for analysis at LBL. Also covered are projects in which the investigator is the only subject and other projects involving individuals, e.g., questionnaires, which may affect psychological balance, civil or legal rights, or privacy.

Any proposed project which will involve human subjects must have approval before the project is initiated. Wherever possible and in order to avoid delays in a project, this approval should be obtained at the time a proposal is submitted. LBL has arranged a procedure with the UC Berkeley Committee for Protection of Human Subjects and has established ~~LBL also has~~ an Advisory Committee to assist the CPHS. All requests for approval should be directed to the Associate Director for Administration, not to the CPHS on the Campus. A minimum of ~~30~~ 45 days should be allowed for review of protocols by the Committee which meets monthly. ~~submissions must be scheduled ahead for the monthly meetings.~~

All investigators are asked to give their close attention to the matter of protection of human subjects. Implementing procedures are furnished separately, and inquiries should be directed to the Associate Director for Administration.

1089502

George L. Pappas
Associate Director