

STANFORD SYNCHROTRON RADIATION LABORATORY

May 21, 1986

TO: W. Gough, Director
DOE Stanford Site Office

FROM: A. Bienenstock, Director *A. Bienenstock*

SUBJECT: Safety Analysis of the Non-invasive Angiography
Experiment

Enclosed is the Safety Analysis Review package for the non-invasive angiography research program to be performed at SSRL on Branch Line IV-II. The analysis of safe radiation doses is the purview of the Medical School's Committee for the Protection of Human Subjects in Research, whose approval letter of April 1, 1986 is enclosed.

We report, therefore, on the other aspects of the system (interlocks, chair, etc.) necessary to assure the safety of the patient. Our analysis, performed by SSRL Safety Office J. Cerino, indicates that the risk to the patient is low.

The SLAC Radiation Committee, as discussed in the enclosed memo of April 15, 1986 from SLAC Director B. Richter, reviewed and approved the proposed experiment. Its review was aimed at seeing that devices and procedures were in place to assure that the subject did not get an accidental dose beyond that planned as part of the experiment itself.

Hence, I have concluded that the hazard classification of this facility is low, and have authorized performance of the experiments.

REPOSITORY Stanford Site Office (SSO)
COLLECTION SSRL 284-2 Human Research
BOX No. N/A
FOLDER SSRL 284-2 Human Research

S S R L M E M O R A N D U M

Date: May 16, 1986

TO: A. BIENENSTOCK

FROM: JOHN CERINO

SUBJECT: ANGIOGRAPHY SYSTEM OPERATIONAL REVIEW

The following persons met today to review the human angiography operation and procedures:

From SLAC: J. Jasberg, G. Nelson, G. Warren;
From SSRL: J. Cerino, R. Hettel, C. Troxel
From Angiography Group: A. Thompson.

The specific objectives of the group were to:

1. Examine each identifiable hazard to the human research subject, and identify the specific mitigation of it;
2. Establish the operational and check-out procedures necessary to assure safe operation.

Using a fault tree drafted by Cerino, the group conducted the review and generated the following action items:

1. At least 1 physician will be in attendance; the exposure will be performed by a California licensed Radiologist, who will be the person to actually operate the Scan Switch.
2. An attempt will be made by Troxel to improve the hutch ventilation. He will install an emergency light in the patient portion of the hutch.
3. The patients will be acquainted with the emergency exit location of Bldg 131 and be told the sound of the fire alarm.
4. The complete interlock and control system, in its final configuration, will be cycled 100 times without failure before the first human exposure.
5. Hettel and Troxel will develop a check-out protocol for the interlock system and it will be performed by one of them prior to each new patient exposure. Subsequent to that check-out no access will be permitted to the monochromator or drum/shutter tank until the human exposure is complete. A signed record of the check will be made.
6. There will be a one-time calibration of the beam monitors against TLD's. Prior to each patient exposure a cross check of the 2 monitors and the SPEAR beam current will be made.

0021445

7. Al Thompson presented a draft experimenter check list for review. The check-out will be performed by 2 members of the experimental team prior to each new patient exposure. A signed record of the check will be maintained in the experimental log with copies to Cerino. Photocopies of the chronological experimental log relating to human exposures will be given to Cerino for record.

There will be a demonstration of the complete system at 10:00 am on Monday May 19.

cc:
attendees
file

DATE: April 16, 1986

TO: Edward Rubenstein, M.D.
Department of Medicine

FROM: Kathy McClelland *K.M.*
Human Subjects Committee

SUBJECT: Assurance approval

Stanford University has an approved assurance with the Department of Health and Human Services for a period of five years. The assurance identification number is M 1272, and our institutional review board's identification numbers are 01XB and 02XM. Our assurance will expire December 31, 1989 and a new assurance will be negotiated prior to this date.

Please let me know if I can furnish any more information that you may need.

cc: ✓ Bill Wilken
SLAC

0021447

1985-1986

<u>Name</u>	<u>Department and Area of Expertise</u>
Carlos A. Camargo, M.D. Associate Professor (Clinical)	Medicine Endocrinology
William T. Clusin, M.D. Assistant Professor	Medicine Cardiology
John Dodson Reverend	Public Member
Don R. Goffinet, M.D., Chairman Associate Professor	Radiology Radiation Therapy and Cancer Research
Kathy Hoare, DNS	Nursing Administration
Sharon Kotabe, Pharm.D. Supervisor	Stanford Pharmacy
Jean Kutner	Student Human Biology
Kathy McClelland	Staff Coordinator
David Oakes, M.D. Associate Professor (Clinical)	Surgery General Surgery
Elwood C. Pierce Director of Operations	Administration
Carole Runyan Price Associate Director Stanford University Hospital	Staff Legal Representative
Peter Rosenbaum, M.D. Professor	Psychiatry Schizophrenia & Psychotherapy
Hans Steiner, M.D. Physician Specialist Clinical Asst. Professor	Psychiatry Child Psychiatry Adolescent Psychiatry & Eating Disorders
David Stevenson, M.D. Associate Professor	Pediatrics Neonatology
George Tidmarsh	Student M.D. Program

0021448

J. Cerin

RECEIVED

APR 16 1986

SLAC MEMORANDUM

SSRL

April 15, 1986

TO: A. Bienenstock

FROM: B. Richter

SUBJECT: Dichromography Experiment

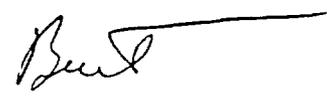
Dear Artie,

This memo concerns the approval of SSRL proposal 456 "Iodine Dichromography with Monochromatic X-ray Beams for Angiography." As you know, the memorandum of understanding and agreement between SLAC and SSRL gives the responsibility for safety at SSRL to SLAC. The dichromography experiment proposes to expose human subjects to synchrotron radiation as part of a medical experiment to test a procedure that may be inherently more accurate and safer than the procedure currently used to diagnose problems with partially blocked blood vessels. Thus the safety issues in this experiment involve medical issues such as dose rate, exposure, etc., as well as the usual issues of radiation safety that are reviewed in the analysis of typical experiments.

The SLAC radiation committee has reviewed this proposal. It's review was aimed at seeing that devices and procedures were in place to assure that the subject did not get an accidental dose beyond that planned as part of the experiment itself. Various modifications to apparatus and procedures were required, and I understand that these have now been implemented. Recently the last analysis required for this experiment, the ray trace analysis, has been received by Gary Warren, analyzed by him and approved. With this the work of the radiation committee is complete.

The final element required for the approval of this proposal is the approval by the University's panel on experimentation on human subjects. Our safety office has just received a copy of the approval by this panel, and so you have our permission to proceed.

BR:k



- cc: A. Boyarski
- G. Warren
- E. Rickansrud
- W. C. Gough

0021449

→ Prof. A. Bienkowski
SRL

DATE: April 1, 1986

TO: R. Hofstadter, M.D.,
E. Rubenstein, M.D., D.C. Harrison,
J. Giacomini, M.D. & H. Gordon, M.D.,
Department of Medicine

FROM: Chairman, Medical Committee for the
Protection of Human Subjects in Research

PROTOCOL ENTITLED:

Revision of: K-edge Angiography with Synchrotron X-rays.
Grant title: K-edge Subtraction Angiography with Synchrotron X-rays.

The Committee approved human subject involvement in your research project on April 1, 1986.

The expiration date of this approval is January 6, 1987. If this project is to continue beyond that date, please submit an updated proposal in advance for the Committee's re-approval. If this proposal is used in conjunction with any other human experimentation or if it is modified in any way, it must be re-approved for these special circumstances. In addition, the Committee requests prompt notification of any complications which may occur during any experimental procedure.

All continuing projects and activities must be reviewed and re-approved at least annually by the Committee. Committee approval of any project is for a maximum period of one year. It is the responsibility of the investigator to resubmit the project to the committee for annual review.

for Kathy McClelland
Don R. Goffinet, M.D., Chairman

cc: Sponsored Projects
Marshall O'Neill

Funding Agency: (NIH HL29024; NIH HV38039; DOE DE-AT03-84ER60200)
Period of Time: 04/01/86-01/06/87
Investigational New Drugs: N, N/A
Investigational New Device: Y
Cooperating Institution: N

0021450

needed in the typical arteriogram procedure). The absolute risk of malignancy resulting from the organ dose estimates given above is a chance of less than one in 30,000 subjects.

I believe that this information, along with the details of the protocol and modified consent form, should be submitted to the Institutional Review Committee for their evaluation and approval.

RAF/eh

cc: JMBrown/SM(M) Committee member to review X-ray Dose/Risk Estimate
WmHMarshall / ditto

REQUEST FOR INSTITUTIONAL APPROVAL OF PROJECT INVOLVING HUMAN SUBJECTS AT RISK
THE MEDICAL COMMITTEE FOR THE USE OF HUMAN SUBJECTS IN RESEARCH

To: Kathy McClelland, 851 Welch Rd., #115 (X5244)

Date: March 6, 1986

PI for Grant/Project:	<u>Robert Hofstadter</u>	MD/PhD	Title:	<u>Professor</u>
Other Investigators:	<u>Edward Rubenstein, M.D.</u>	MD/PhD		<u>Professor (Clin</u>
	<u>Donald C. Harrison, M.D.</u>	MD/PhD		<u>Professor</u>

Title of Research Project: K-edge Angiography with Synchrotron X-rays

(AND GRANT, IF DIFFERENT) K-edge Subtraction Angiography with Synchrotron X-rays

Contract/Grant #	<u>1 R01 HL29024-01-A1</u>	NIH Grant	Period	<u>7/1/83-6/30/86</u>
	<u>1 HV-38039</u>	Sponsor NIH Contract		<u>7/1/83-6/30/86</u>
	<u>DE-AT03-84ER60200</u>	DOE Grant		<u>2/1/84-1/31/87</u>

Investigator's Address Rm. TC-129 Dept. Medicine Ext. 7-7188

Sponsored Un-sponsored Investigational Drug Investigational Device
 IND # _____ IDE # _____

Department Chairman Signature: *Edward Rubenstein*

REVIEW PROCESS - Check One: REGULAR REVIEW PLEASE SEND 4 COPIES TOTAL (DO NOT ST
 EXPEDITED REVIEW PLEASE SEND 2 COPIES (See regulations
 (VA Not Eligible) on reverse side of this form)
 Paragraph number under which expedite
 review is requested.

APPROVAL OF THE HUMAN SUBJECTS COMMITTEE SHOULD BE OBTAINED PRIOR TO SUBMISSION OF THE RESEARCH PROJECT TO HHS/NIH. THE COMMITTEE MEETS THE FIRST TUESDAY OF EVERY MONTH AND REVISION APPLICATIONS SHOULD REACH THE COMMITTEE 15 DAYS PRIOR TO THE MEETING DATE.

PLEASE PROVIDE INFORMATION IN THE FOLLOWING AREAS AND ATTACH TO THIS FORM:

- Describe Any Changes Since Original Approval.
- Attach the Consent Form(s) You are Using for this Study.
(Even if it is the same as previously approved.)

REVISION

Request for Institutional Approval of the Protocol Entitled:
"K-Edge Subtraction Angiography with Synchrotron X-rays"

Additional Information:

1. Describe Any Changes Since Original Approval.

The consent form has been modified to provide more detailed information about risks related to the venous catheterization procedure and to the radiation exposure. Corrected parameters for contrast agent administration have been provided.

A report from Roland Finston is appended in which he provides additional information regarding radiation exposure.

2. Consent forms are attached.

0021454

FILE

DATE: February 11, 1986

To : Roland Finston, Director
Health Physics
FROM : Edward Rubenstein, Robert Hofstadter and Donald Harrison

SUBJECT: Research Project: K-edge Angiography with Synchrotron Radiation

Thank you for your willingness to participate in the review of the radiation safety issues involved in the synchrotron-radiation-based angiography project at SSRL.

We would like to respond to the questions you raise in your memo of February 11, 1986.

The original protocol documents submitted to the Human Subjects Committee were based on data available at that time. We now are able to make better estimates of the parameters related to exposure to X-radiation.

The images will be recorded in a line-by-line process, each recording constituting a frame. The horizontal dimension of each frame is that of the synchrotron radiation beam, which is 123 mm. The vertical dimension of the frame will vary depending upon the size of the patient, but will usually be from 10-15 centimeters.

For coronary angiography, we currently plan to record images in three projections: lateral, left anterior oblique and right anterior oblique. The precise angles of the oblique projections will be determined by the coronary artery anatomy as established on arteriograms done by the conventional method in the recent past on each patient.

In the initial studies, a sequence of frames will be recorded to establish the flow characteristics of the bolus of contrast agent. This will probably require five to seven frames, taken with the patient in one position. Thereafter, one or two frames will be recorded with the patient in the other two positions.

The parameters that determine the scan speed are the detector element size (0.5 X 0.5 mm), the velocity of cardiac motion, and the x-ray flux. We currently plan to record images either at a rate of 4 msec per line or 8 msec per line, depending upon the available electron current in the storage ring and on the patient's heart rate.

0021455

February 11, 1986

Page 2

The patient consent form has been amended to include the information suggested under item #2 in your memo of February 11th; see attached.

The physicians who will operate the x-ray exposure control apparatus are holders of the permit of the State of California entitled "X-ray Supervisor and Operator."

Images will not be recorded on employees or on other normal subjects. The synchrotron radiation beam is highly collimated naturally but is further restricted in size by collimators that constitute part of the imaging system. The expected radiation exposure for a patient will be measured with an appropriate dosimeter.

We would be grateful to have your comments about the above and to respond to any further suggestions or questions.

ER/aw

bcc: D.C. Harrison
R. Hofstadter

Attached: Informed Consent 2/13/86

0021456

4/24/86

INFORMED CONSENT FOR SYNCHROTRON ANGIOGRAPHY BY MEANS OF VENOUS INJECTION
OF CONTRAST AGENT

You are invited to participate in a study of angiography. You have already undergone angiography by the conventional method, involving arterial catheterization and the direct injection of contrast agents into the arteries. We hope to develop a means of visualizing these arteries without the necessity of physically entering them with needles and tubes. In the presently proposed technique, the contrast agent is injected into veins, instead of arteries, a procedure that is believed to be substantially safer.

If you decide to participate, we will perform an angiographic procedure (coronary, cerebral, other,) by means of a venous injection of contrast agent, employing x-rays produced at the Stanford Synchrotron Radiation Laboratory. You will be given injections into a vein of a radiographic contrast agent, as employed in routine clinical practice. The injection may be given directly into a vein in the arm or may be given into a vein in the chest. In the latter instance a flexible, hollow tube, called a catheter, will be inserted into a vein in an extremity or the neck, and the catheter is then advanced into the chest so that its tip is in a central vein adjacent to the intake chamber (right atrium) of the heart. The contrast agent will then be administered using a power injector, at a rate up to 20 ml/sec and at a dose of up to 0.75 ml/kg of body weight per injection. Following the injection, scanning digital radiographs will be

SSRL

MAY 12 1986

RECEIVED

0021457

taken of the arterial structures being studied. The procedure will probably require 1/2 to 1 1/2 hours. The risks of this procedure include the following: severe allergic (anaphylactoid) reaction to the iodine contrast agent; mechanical tear of a vein; local bleeding; impaired kidney function; reaction to local leakage of dye. The procedure involves minor surgery and entering the blood vessels with special plastic tubes. Leakage or irritation at the site of blood vessel entry may cause local discomfort. Among the complications of the procedure are blood clots, irregularities of the heart beat, heart attack and death. The likelihood of the serious complications is believed to be less than 0.5 percent.

There are risks related to radiation exposure inherent in any x-ray examination, including delayed cancer and genetic change. The exposure from this examination will carry with it a risk equivalent to that from approximately 4 months of natural background radiation. In this examination, approximately eight to ten radiographs (x-ray pictures) will be recorded, and the x-ray exposure of each is similar to the exposure involved in an ordinary x-ray picture of the heart region.

It would be impractical and even misleading to describe in detail all of the possible risks and complications which might result from the procedure. Any questions should be discussed with a member of the angiography team who will be performing the study. This person will review the procedure as is planned for your individual case.

Potential benefits that may be accrued to you relate to information about

the status of the arteries to be studied. Such information might be accumulated without the necessity of performing invasive arterial injections. We can not and do not guarantee or promise that you will receive any benefits from this study.

Any data that may be published in scientific journals will not reveal the identity of the subjects. In the interest of public safety, patient information will be provided to federal and regulatory agencies as required.

There will be no fee charged for the non-invasive angiogram.

Your decision whether or not to participate will not prejudice you or your medical care. If you decide to participate, you are free to withdraw your consent and to discontinue your participation at any time without prejudice to you or effect on your medical care. If you have any questions, we expect you to ask us. If you have any additional questions later, we will be pleased to try to answer them.

In the event of physical injury that arises solely out of the negligence of the employees of Stanford University or of the Stanford University Medical Center or its staff in this study, reimbursement for expenses incurred for necessary medical treatment and hospitalization is available. For further information, please call 497-5244 or write the Medical Center Committee for the Protection of Human Subjects at 851 Welch Road, Room 115, Palo Alto, California, 94304. In addition, if you

are not satisfied with the manner in which this study is being conducted, you may report any complaints to the same telephone number and address.

Persons who participate in a medical experiment are entitled to certain rights. These rights include but are not limited to the subject's right to: be informed of the nature and purpose of the experiment; be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized; be given a description of any attendant discomforts and risks reasonably to be expected; be given an explanation of any benefits to the subject reasonably to be expected, if applicable; be given a disclosure of any appropriate alternatives, drugs, or devices that might be advantageous to the subject, their relative risks and benefits; be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise; be given an opportunity to ask any questions concerning the experiment or the procedures involved; be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice; be given a copy of the signed and dated consent form; and be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

YOUR SIGNATURE INDICATES THAT YOU HAVE READ AND UNDERSTAND THE ABOVE INFORMATION, THAT YOU HAVE DISCUSSED THIS STUDY WITH THE PRINCIPAL INVESTIGATOR(S) AND/OR HIS OR HER STAFF, AND THAT YOU HAVE DECIDED TO

PARTICIPATE BASED ON THE INFORMATION PROVIDED. A COPY OF THIS FORM IS
AVAILABLE TO YOU UPON REQUEST.

PERSONS WHO ARE INTERVIEWED IN A MEDICAL INVESTIGATION SHOULD BE ADVISED THAT

THEY ARE NOT OBLIGED TO ANSWER ANY QUESTIONS.

Signature of the person to be interviewed Date

AND ANY STATE OF MIND TO BE INTERVIEWED IN A MEDICAL INVESTIGATION

PERSONS WHO ARE INTERVIEWED IN A MEDICAL INVESTIGATION SHOULD BE ADVISED THAT

THEY ARE NOT OBLIGED TO ANSWER ANY QUESTIONS.

Signature of Investigator or Witness

Signature of Investigator or Witness
