



U.S. DEPARTMENT OF ENERGY

Stanford Site Office (SLAC/SSRL)
Energy Research Division/SAN
Stanford University
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702598

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APR 21 1986
ESQA DIVISION
COMM: (415) 854-3300
X2261
FTS: (8) 415-470-9040

April 17, 1986

Mr. James T. Davis
Director of ESQA
San Francisco Operations Office
U.S. DEPARTMENT OF ENERGY
1333 Broadway
Oakland, CA 94612

Ralph
Jim
4
4/21

Dear Dr. Jim,

Enclosed for your information is additional background information on the SSRL angiography experiment using synchrotron radiation with human subjects.

Sincerely,

Bill

William C. Gough, Director
Stanford Site Office (SLAC/SSRL)
ER Division, SAN

Enclosed

cc: Dr. Jim Robertson, ER-73 (w/encl.)

FN: M11/DAVIS.LTR

REPOSITORY DOE-OAK
COLLECTION Environment & Safety Sup Div
BOX No. Central Files
FOLDER 1300-3.C Angiography Expt.
at SSRL (1986)

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RECEIVED
APR 17 1986

WGG
Mare
Chris

~~284-2/55~~
284-2/55

SLAC MEMORANDUM

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

0021007

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.

0021008

Roland Finston
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

0021009

REVISION

protocol #

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 (Clinical)</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>	Sponsor	<u>NIH Grant</u>	Period	<u>7/1/83-6/30/86</u>
	<u>1 HV-38039</u>		<u>NIH Contract</u>		<u>7/1/83-6/30/86</u>
	<u>DE-AT03-84ER60200</u>		<u>DOE Grant</u>		<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 STAPLE)
 EXPEDITED REVIEW PLEASE SEND 2 COPIES (See regulations
 (VA Not Eligible) on reverse side of this form)
 Paragraph number under which expedited 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:

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

4/8/86

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

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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. After analyzing the results of this examination, your physician may recommend that you undergo the alternative procedure, that of routine angiography employing arterial catheterization and direct injection of radiocontrast agents into the arteries.

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

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.

Signature

Date

Signature of Investigator or Witness

11/81

0021013

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

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

injection. Following the injection, scanning digital radiographs will be 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.

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.

0021018