

TA-UG-0001
Rev: BASIC

Kennedy Space Center
Human Research
Institutional Review Board
Handbook

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Acronyms and Abbreviations:

ACLS	Advanced Cardiac Life Support
BP	Blood Pressure
CPR	Cardiopulmonary Recussitation
ECG, EKG	Electrocardiogram
EMG	Electromyogram
EMS	Electrical Muscle Stimulation
FDA	Food and Drug Administration
H&P	History and Physical
IDE	Investigational Device Exemption
IND	Investigational New Drug
IOP	Internal Operating Procedure
IRB	Institutional Review Board
KMI	KSC Management Instruction
KSC	Kennedy Space Center
LBNP	Lower Body Negative Pressure
MD	Medical Doctor
NASA	National Aeronautics and Space Administration
NPD	NASA Program Directive
PI	Principal Investigator
PVC	Premature Ventricular Contraction
RN	Registered Nurse
TMX	Treadmill Exercise
VO2	Volume of Oxygen consumed per minute

1.0 INTRODUCTION

1.1 Objective

The objective of the Kennedy Space Center (KSC) Human Research Institutional Review Board (IRB) is to protect human subjects in research performed by KSC by ensuring that risks to the health and safety of subjects are minimized, that any residual risks are warranted by the anticipated benefits of the research, that all participants are fully informed of the risks and voluntarily consent to participate, and that the privacy and confidentiality of subjects are protected.

1.2 Authority

The authority for and responsibilities of this Board derive from NPD 7100.8, "Protection of Human Research Subjects," KMI 1150.2, "Boards, Committees, Working Groups, and Panels," and the "KSC Human Research Institutional Review Board Charter."

1.3 Scope

All research involving human subjects performed at KSC, or which is conducted by KSC (NASA or contractor) personnel, or which receives funding from KSC, is subject to KSC IRB review, except for flight experiments approved by the JSC IRB utilizing JSC personnel as subjects.

1.4 Definitions

Principal Investigator (PI)– The researcher designated as responsible to the IRB for the conduct of a study involving human subjects.

Investigators – Personnel with scientific training who plan and conduct a study.

Technical Personnel – Personnel other than the investigators who assist in the conduct of a study.

Minimal risk – The risk associated with normal duties and with routine medical examinations and tests.

2.0 IRB COMPOSITION AND MEMBERSHIP

2.1 Permanent Member

Permanent members of the Human Research IRB will include, at a minimum:

The Chief, Aerospace Medicine and Occupational Health Branch, who will be the chair of the IRB.

A Co-Chair, who may be one of the members listed below:

The KSC Chief Medical Officer

A KSC representative with scientific or medical training who will serve as executive secretary

A representative of the KSC Office of the Chief Counsel (CC)

A representative of the Safety, Health, and Independent Assessment Directorate (QA)

A representative of the Spaceport Engineering and Technology Directorate (YA)
A representative of the Workforce and Diversity Management Office (BA)
A member appointed from outside KSC

2.2 Alternate members

Alternate members may be appointed for each of the permanent members, and may take their place if a permanent member is not available.

2.3 Temporary Members/Consultants

Temporary Members/Consultants provide information to the IRB and may participate in the discussion and evaluation of a specific protocol, but do not vote. They are appointed by the Chair for the evaluation of specific protocols, for purposes of:

- 1) Providing expertise in a specialized discipline, such as radiation exposure, diving, etc.
- 2) Acting as an advocate for a specific group of potential subjects

2.4 Appointment:

All members of the IRB will be appointed by the KSC Center Director, based on the recommendations of the KSC directorates and offices represented on the IRB. IRB appointments are for an indefinite period.

2.5 Training

Members of the IRB will be familiar with the contents of this handbook and its appendices, and other training materials as will be defined in the KSC Bioethics Training Course. Some of these resources are identified in Appendix 2C.

3.0 IRB MEETINGS AND RECORDS

3.1 Meeting Schedule and Notification

Meetings of the IRB will be convened at the discretion of the Chair:

- 1) At least annually to review ongoing or newly proposed research.
- 2) As needed during the year to review new proposals or proposal modifications.
- 3) Upon request of an investigator, subject, or other interested party to review an anomalous occurrence or potential hazard.

Notification of each meeting will be provided to the KSC Chief Safety Officer.

3.2 Quorum and Essential Personnel

A majority of the voting members, including the Chair or the Co-Chair must be present to hold an IRB meeting and vote.

3.3 IRB Records

The IRB will maintain a record of the agenda and minutes of each meeting and the research proposals and proposal modifications it receives.

The vote of the IRB on each proposal will be recorded in the minutes. The IRB minutes will be posted in the KSC Business World web archive, and will be provided in electronic format to the Safety and Health Council (SHC) Secretary and the Continuous Improvement (CI) Specialist.

3.4 Status Reports

3.4.1 Report to the Health and Safety Council

The IRB will submit a semiannual status report to the KSC Health and Safety Council identifying major accomplishments, major problems identified and the status of any major issues,

3.4.2 Report to NASA Headquarters

The IRB will submit an annual report to NASA Headquarters giving a summary of proposals received, incidents involving test subjects, corrective actions, and any actions taken against an Investigator or proposal.

4.0 EVALUATION AND APPROVAL PROCESS

4.1 Written Proposal

The PI will provide the completed written proposal to the board at least two weeks prior to the board meeting. The format for a KSC Human Research Proposal is given in Appendix A, and for a typical consent form in Appendix B.

4.2 Presentation

At the IRB meeting, the PI will briefly discuss the study and answer any questions the board may ask. Potential changes to the protocol may be discussed but will normally not be approved/disapproved until presented in writing, except for limited modifications recommended by the Board, and agreed to by the Investigator, which can, with the approval of the Chair, be entered directly in the minutes. In this case the Investigator will be provided with a copy of the change.

4.3 Voting

Following the presentation and clarifications, the board will meet privately and discuss and vote on the proposal. A member may abstain, e.g., if a potential for a conflict of interest exists, or if the member is not familiar with the proposal. An IRB member who is named as an investigator in a proposal will not participate in its approval except to provide information as requested.

4.4 Disposition

The proposal may be approved by majority of members present, may be disapproved, or approval may be deferred pending submission and review of modifications.

4.5 Notification

The Chair will notify the PI of the disposition following the IRB meeting.

4.6 Protocol Modifications

The IRB may approve a modification to an approved protocol by presentation and vote at a regular meeting, or by expedited review.

4.7 IRB Evaluation by Expedited Review

The IRB may review protocols in an expedited fashion, as determined by the Chair. This may be done in one of two ways:

- 1) The Chair reviews the proposal and determines the disposition.
- 2) The Chair solicits comments and a vote of the members (or a subset thereof) by email, telephone, or other means.

Expedited review is normally used only for protocols with minimal risk, or for limited changes to existing protocols. Approvals by expedited review are reported to the full IRB by correspondence and at its next regular meeting.

4.8 Reporting of Anomalies or Injuries

4.8.1 Reporting Procedure

In the event of an injury to a subject, or the occurrence of an anomaly in equipment or subject response, which indicates that the risk of subject injury is significantly greater than that described in the approved protocol, testing will be terminated and the PI will make a report to the Chair of the IRB as soon as practical. This report may be verbal, but a written summary should be submitted promptly, together with the corrective actions to be taken.

The requirements for reporting an injury or close call involving a research subject are the same as if the incident involved an employee during normal duties. The organization or contractor supporting the research will submit the applicable reports to OSHA, NASA, KSC, and/or the contractor reporting system.

4.8.2 Approval to Proceed

The IRB may give permission to resume the study after reviewing the written report submitted by the PI, and any changes in the protocol required by the anomaly. If, in his judgment, the anomaly is clearly understood and has been corrected so as to eliminate the unexpected risk, the Chair may approve the protocol, as modified, by expedited review.

The IRB may elect to:

- 1) Allow continuation of the study

- 2) Allow continuation of the study with approved changes
- 3) Not allow continuation of the study

4.9 Annual Review

The PI of each currently approved research project should present an annual report to the IRB on a date set by the Chair to provide the status, results, any anomalies, and future plans of each active proposal.

4.10 Sanctions

As authorized by NPD 7100.8C (See Appendix 3D), sanctions may be imposed on any investigator who does not comply with the policies and procedures required by NASA or with the research protocol as approved by the IRB. These include:

4.10.1 Suspension of protocol

The IRB or its Chair may direct that any human research protocol be immediately suspended if it fails to meet the requirements of the IRB, or if there is any indication of scientific misconduct, unethical practice, or an unacceptable level of risk to subjects.

4.10.2 Recommendation of Investigation

The IRB may vote to recommend a formal investigation of an incident or significant adverse event.

5.0 CRITERIA FOR IRB APPROVAL OF HUMAN RESEARCH

This section describes the minimum elements required in a research proposal in order to receive IRB approval.

5.1 Safety

5.1.1 Minimization of Risk

Human research procedures performed at KSC must be designed so as to keep any risk of injury, illness, or other adverse effect on human subjects to the minimum level that is feasible. In general, the risk should not be significantly greater than that which might be encountered in normal duties. In this context, the term "normal duties" may include tasks that are physically demanding or entail potential hazards, but which are safe to perform with proper equipment, training, and procedures.

5.1.2 Residual Risk Warranted

Residual risk, which cannot be eliminated, should be warranted on the basis of the potential benefits of the research, although there may be no benefits to the subject personally.

5.1.3 Safety Analysis

Where a device or system is employed which could, through a potential failure, endanger the subject, a safety analysis should be performed and included in the proposal. This analysis should be approved by a safety professional from the organization conducting the research or NASA.

Protocols requiring exposure of research subjects to radiation will be submitted to the KSC Radiation Protection Officer, who will provide an assessment to the IRB.

5.2 FDA Approval

5.2.1 FDA Approval of Drugs

FDA approval may be required for the use of a drug or medical device in research. An FDA Investigational New Drug (IND) exemption is required if using a drug not approved by the FDA for use in the United States, or if using a drug at dosages that would not be considered acceptable under the existing approval (See Appendix 5A). Use of an approved drug and dosage, for an indication different than that specified by the FDA, does not normally require IND approval.

5.2.2 FDA Approval of Medical Devices

If a study utilizes a device not currently FDA approved that affects the physiology of the subject, the IRB must determine if the use of the device as specified in the protocol presents a non-significant risk (NSR) or a significant risk (SR). If use of the device poses a significant risk, an application for an investigational device exemption (IDE) must be submitted to the FDA. If the risk is found to be non-significant, the use of the device is permitted without submitting an IDE application. In cases where question exists as to whether an IDE is required, the IRB may consult the FDA for clarification.

5.3 Equitable Subject Selection

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The research plan should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for recruitment and selection of such subjects.

5.4 Informed Consent

All subjects must give informed consent to participate as subjects. The subject must receive a written and verbal description of the tests, procedures, or other study activities in which he will be asked to participate. An example is given in Appendix 1B. This explanation must include a description of any risks or discomfort the test may impose. The explanation must be understandable to the subject, and any questions must be answered. Generally the subject briefing must be presented by one of the investigators performing the study.

If, following this explanation, the subject wishes to participate in the study, he/she and the investigator must complete the subject consent form. A typical subject briefing and informed consent form is given in Appendix B.

5.5 Medical Screening

Medical Screening of subjects is required for all studies, which impose physiologic stress.

Medical screening for subjects will be in accordance with LSSC BIO-IOP-001. Based on the degree of physiologic stress imposed by the study, subject screening may include one or more of the following: Medical history, physical examination, laboratory tests, and cardiovascular stress test. Generally, for any study, which may require near-maximal cardiovascular exertion or LBNP beyond 20 mmHg, a maximal stress test is required.

If the subject has had physical examination and/or stress test as part of his/her normal duties, it may be accepted as evidence of qualification. A stress test conducted for other purposes may be accepted provided the subject was exposed to a stress level equal to or greater than will be imposed by the study.

Medical screening must be repeated at least annually, except for stress tests, which must be repeated at least every three years.

5.6 Medical Monitoring

During tests that impose significant physiologic stress on any body system may require monitoring by a nurse, physician, or other personnel as approved by the IRB. Medical monitoring will be in accordance with LSSC Internal Operating Procedure BIO-IOP-001 (see Appendix 6A).

Maximal physiologic stress is hazardous in that it can lead directly to death or disability through hypotension, heat stress, etc. and may also cause the subject to collapse, resulting in trauma. The medical monitor serves two roles in minimizing this risk. The primary duty of the monitor is to observe the subject visually and by instruments to identify the approach of maximal stress, and to terminate the test immediately if the subject approaches a physiologic limit, or if any other medically hazardous condition occurs. In certain cases, such as the performance of a screening maximal treadmill test or maximal LBNP, both a nurse and physician may be required. There are certain protocols in which medical monitoring may be provided by a nurse on-scene and a physician on call for consultation.

The secondary duty of the medical monitor is to provide advanced life support to the subject, in the unlikely event that a hazardous medical condition does occur, until emergency medical services arrive. In the unlikely event that a medical emergency occurs in a case when no medical personnel are physically present, personnel at the scene should call 911 without delay. Medical personnel elsewhere in the building may then be summoned to assist as available until emergency personnel arrive.

Medical monitoring may initially be required because the level of stress imposed by a new test is not known. In the course of the study a point may be reached where all the subjects have experienced the test conditions at least once, and can be clearly seen not to be approaching physiologic limits or encountering other hazards. When sufficient experience is available the PI may request that the IRB consider a modification to the protocol to modify or delete the medical monitoring requirement.

The medical monitor is also required to ensure that the experiment is at all times conducted in accordance with the approved protocol. The monitor must therefore be familiar with the protocol as approved by the IRB. In the event that, in the opinion of the medical monitor, the protocol departs from the parameters and procedures approved by the IRB, the medical monitor shall terminate the test. If the test cannot be conducted within the parameters previously approved, the IRB Chair shall be notified and, if appropriate, a request for modification of the protocol may be submitted.

5.7 Test Readiness Review

Before performing any test in which errors in procedure or equipment function could jeopardize subject safety, the investigator conducting the test will perform a test readiness review, to include verifying the safe operating condition of equipment and the readiness of the subject and test personnel. The checks to be made during the test readiness review will be noted in the procedure section of the research proposal.

5.8 Liability Insurance

The proposal must state whether liability insurance is provided for potential injury or death of research subjects. If such insurance is provided, the source and amount must be stated. For example, in protocols supported by LSSC such coverage is generally provided under the LSSC general liability insurance policy. Subjects must be informed whether or not such compensation is provided.

5.9 Privacy of Medical Data

In accordance with NMI 7100.8B, biomedical data, if retrievable by personal identifier, is subject to the Privacy Act and is maintained under the requirements stated in Appendix 3F, "NASA System of Records, NASA 10 HERD, Human Experimental and Research Data Records."

Normally this requires that all experimental data with subject identifiers must be stored in a secured area such as a locked file maintained by the LSSC. Investigators who take data to other locations must either maintain the data in secure storage and limit access to the research personnel identified in the proposal, or they must remove all information identifying subjects by name, social security number or similar traceable personal information from the research data.

Information that could reasonably be used to identify individual subjects must be excluded from any research data that is published, presented, or otherwise released to the public.

Appendix 1- Submissions by the Investigator to the IRB

Appendix 1A

KSC Human Research Proposal

1. Study title and date of submission

2. Organization conducting the study

The contractor, NASA organization, university or other entity, which will be directly responsible for performing the human research procedures.

3. Scientific and technical personnel

List the principal and participating investigators and technical personnel, and their institutions.

4. Study objective, hypothesis, and scientific rational

Describe the goals and scientific rational of the study and the potentially useful information that is expected.

5. Justification for use of human subjects

Identify the requirements that can be met only by a human experimental study as opposed to historical studies, physiologic modeling, or other approaches. Show that the potential benefit of the study is sufficient to warrant any residual risk to which the subjects may be exposed. Verify that subject selection will be equitable with regard to race, gender, and ethnicity or identify and justify any constraints on subject selection.

6. Study plan and schedule

Give planned start and completion dates for the human research.

7. Equipment and procedures

This section should concisely describe the equipment and devices that will be used in conjunction with human subjects, and the procedures, which will be performed on human subjects.

8. Possible inconveniences, discomforts, illness, pain and risk to subjects

Describe the expected discomfort and stress imposed on the subjects, and any foreseeable potential adverse effects on the subjects from unusual reactions to the physiologic stresses of the study, unexpected failure of the experimental apparatus or procedural errors.

9. Hazard controls and safety precautions

Describe the design features, protective equipment, and procedures, including test readiness reviews, which will be followed to minimize subject discomfort and residual risk. State the medical circumstances under which tests will be terminated and the procedure that will be followed for terminating the test. If a formal safety review or analysis is required it should be attached.

10. Medical evaluation of subjects

Criteria used to approve subjects for initial participation, and any other medical evaluation planned during the course of the study.

11. Medical monitoring and response to contingencies

State the requirements, if any, for medical personnel to observe the subject during each procedure. If medical personnel are required to be on call, give the required response time. Identify any contingencies, under which emergency medical services will be requested, and procedures and response time if this is required.

12. Subject compensation

Wage, salary, or other compensation to the subject for participation

13. Liability insurance

Source, description, and maximum amount of compensation to be received by a subject or the subject's legally authorized representative in the event of injury or death. If the subjects are recruited and paid by the LSSC, this will normally be provided through the LSSC liability insurance policy.

14. Information provided to potential subjects

This section (commonly included as an attachment) is a description of the study provided to prospective subjects prior to their signing the consent form. It should explain any stresses, discomforts, or risks the subject will experience. This should include actions the subject is expected to perform, including the reporting of any problems and the circumstances (i.e. level of discomfort) and method (i.e. verbal statements, hand signals, etc.) by which the subject should request that a test be stopped.

15. The Human Research Consent Form

This is normally supplied as an attachment and is a copy of the form signed by the subject, witness, and investigator. The form should include the statement that participation is voluntary and the subject is free to withdraw at any time.

16. Management of confidential data

Describe the plan for ensuring privacy and protecting the confidentiality of subject medical data on paper or in electronic form.

17. Training in ethical treatment of subjects

Document that the principal investigators have received appropriate training in ethical treatment of research subjects by familiarity with Appendix 2 of the KSC IRB Handbook or equivalent training.

18. Financial Interests

Please identify any financial interests in this study on the part of the investigator(s) or organization(s) supporting this research.

Attachments:

- 1. Subject briefing*
- 2. Subject consent form (may be combined with the subject briefing)*
- 3. Detailed test procedure*
- 4. Approvals of the protocol by institutional review boards of other organizations, if any*
- 5. Scientific references, documentation, or discussions, if required*

Appendix 1B

Study Description for Prospective Subjects *[sample]*

Title: Eye movement and motion perception induced by off-vertical axis rotation

Our ability to move without falling depends on the brain's ability to use available sensory information to control our body movements. The balance (vestibular) system in the inner ear senses different types of movements and helps us know our position in relation to the direction of gravity, for example when we tilt our head. Movement in an altered gravity environment drives the brain to learn new ways of orienting oneself. In the absence of gravity, the balance organs do not sense head tilt in the same way but continue to sense translational head motion. It has been hypothesized that after surgery, the brain may misinterpret changes in head tilt position.

The purpose of our research is to examine adaptive changes in balance function that occur after surgery. This research is specifically focused on the sensory organs in the inner ear (otoliths), which serve to detect linear accelerations from translational or tilt stimuli. We infer changes in otolith function from eye movements and perception reports during rotation about a tilted axis.

PROCEDURES

You will be asked to participate in three study sessions. Each session will last one hour, with the exception of the first session which will include an additional 30 minutes for familiarization and fitting procedures described below.

You will be asked to avoid provocative training exercises or unusual motion stimuli (e.g., sea travel, amusement rides, non-commercial air travel) for 24 hours prior to any session. You will be asked to avoid alcohol for 24 hours prior to any session. The tests will be scheduled in the morning if possible since responses are altered by fatigue.

During this test your eye movements will be measured using video cameras as you are exposed to different rotational and tilt stimuli. Your motion perception will be recorded with a joystick device and by verbal reports. You will be positioned in a chair sitting upright, and straps and formable padding will be used to help restrain you securely and comfortably in the chair and minimize pressure points. The head restraint system will apply pressure to custom-fitted thermoplastic pads, which will be positioned with the aid of a skullcap. These head pads will be molded during your first test session. At the beginning and end of the test you will be asked to look at visual targets to calibrate the eye measurement system. The room will then be darkened, and masking noise will be provided over a chair-fixed speaker to minimize auditory cues. The chair will be tilted 10° from the vertical, and then you will be rotated at a constant speed of 45 °/sec in either the clockwise or counter-clockwise direction. Initially as you rotate about the new

tilt axis, you will be asked to look straight ahead in darkness as your eye movements are recorded. You will then describe your motion perception. The experiment will proceed with measurements at 20° tilt axis at 45 deg/sec and 180 deg/sec until the rotator is returned to an upright position and stopped. During the acceleration from one speed to another, you may be asked to fixate on a small target placed in front of you. After completing the first rotation, rotation in the opposite direction will be performed. All chair accelerations and decelerations will not exceed 30 deg/sec/sec.

RISKS/DISCOMFORTS

The primary medical risks and discomforts associated with the tilt rotator will be motion sickness. The severity of symptoms will vary across individuals. The speed and tilt angles have been chosen to minimize problems with motion sickness. In a previous experiment with chair velocity of 60°/s and tilt angle ranging from 9° to 15°, motion sickness symptoms occurred with only 21 out of 550 subjects tested. Except for 2 subjects who suffered from vomiting, most of them felt only slight symptoms (sweating, pallor, stomach awareness). If you experience motion sickness symptoms, the test will be terminated. You will have constant two-way audio communications with the test operator to provide verbal perception reports and reports of any symptoms.

Other discomfort may result from pressure points associated with the restraint systems. The formable head cap pads will be used to minimize pressure points and discomfort for the head restraint. These pads will need to be heated to make them pliable for the fitting, and care will be taken to ensure they are temperature-safe to touch. Quick-release mechanisms have been employed where appropriate to ensure reasonably quick egress. Other steps taken to ensure safety include marking off the rotational envelope, and ensuring the structural integrity of each component during assembly. Sensors in the rotator are provided to shut the system down in case of a run-away failure mode. The illumination source for the cameras use low levels of near-infrared (IR) light so as to record your eye movements in darkness. There is a slight chance of lens and cornea damage from too much near-IR exposure, and care has been taken to ensure the exposure levels are within safe thresholds. There is also a chance of eye injury from prolonged exposure to the laser pointer used to align the calibration targets; however, the calibration procedure is relatively short and you will control when the laser is turned on (via an activation button).

BENEFITS

You will receive no direct benefit from participation in this study, but your participation may help the investigators better understand how the brain substitutes for the absence of inner ear receptors in processing of sensory information. The test protocol has been used as a clinical diagnostic tool for assessing inner ear function, and may prove useful in assessing the readaptation of astronauts upon return to earth's gravity.

FINANCIAL COSTS AND PAYMENTS TO SUBJECTS

You will be compensated for your expenses for participation, such as travel. In addition you will receive \$50 upon your completion of your portion of the study.

Appendix 1D

Request to Renew Approval of Human Research Protocol

Submit to: David A. Tipton, MD, Chair
Kennedy Space Center Human Research IRB
Mail Code TA-C2
Kennedy Space Center, FL 32899

Protocol Title:
Date Initially Approved:
Investigator:
Address:

Phone:
Fax:
Email:
Sponsoring Organization:
Organization(s) Performing Study:
Estimated Date of Completion:
Subjects Currently Enrolled:
Additional Subjects Required:
Number of Subjects Withdrawn, and Principal Reasons:

Adverse Events to Date:

Additional Risks Identified:

Preliminary Results:

Estimated date of Completion:

Appendix 2 - Basic References in Research Ethics

Appendix 2A - Belmont Report

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.

Joseph V. Brady, Ph.D., Professor of Behavioral Biology, John Hopkins University.

Robert E. Cooke, M.D., President, Medical College of Pennsylvania.

Dorothy I. Height, President, National Council of Negro Women, Inc.

Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.

Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.

Karen Lebacqz, PhD., Associate Professor of Christian Ethics, Pacific School of Religion.

*David W. Louisell, J.D., Professor of Law, University of California at Berkeley.

Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.

Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.

*Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.

*Deceased.

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Belmont Report

Ethical Principles and Guidelines for Research Involving Human Subjects

Scientific research has produces substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the

Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes² intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment, or therapy to particular individuals.³ By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated in a formal research project.⁴

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity

requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression “basic ethical principles” refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect for persons, beneficence, and justice.

1. Respect for Persons – Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons’ considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person’s considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual’s life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities, which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to “volunteer” or to “protect” them presents a dilemma. Respecting persons, in most hard cases is often a matter of balancing competing claims urged by the principle of respect itself.

2. *Beneficence.* – Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term “beneficence” is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim “do no harm” has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients “according to their best judgment.” Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children – even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without such research being inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. *Justice.* – Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of “fairness in distribution” or “what is deserved.” An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to

individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project; long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conduct of research lead to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. - Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

2. Information. - Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include; the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently

invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that: (1) incomplete disclosure is truly necessary to accomplish the goals of the research; (2) there are no undisclosed risks to subjects that are more than minimal; and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

3. *Comprehension.* - The manner and contest in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest. *Voluntariness.* An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contract, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence – especially where possible sanctions are involved – urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

4. Assessment of Risks and Benefits. – The assessment of risks and benefits requires a careful array of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons.

The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated

benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

5. *The Systematic Assessment of Risks and Benefits.* - It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the follow considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject – or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

6. *Selection of Subjects.* - Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection or research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on

the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

[FR Doc. 79-121065 Filed 4-17-79; 8:45 am]

7. Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare. Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

8. Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a

particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

9. Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

Appendix 2B

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for

themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research that may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional

affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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Appendix 2C - Training Resources in IRB Procedures and Bioethics

KSC IRB Training Course

The IRB Training Course will be revised periodically. At the present time it is recommended that IRB members review the contents and appendixes of this handbook and the KSC IRB website below, focusing on the areas relevant to their roles in the IRB and to research conducted at KSC.

KSC IRB Website:

<http://medical.ksc.nasa.gov/irb>

Appendix 3 - Federal and NASA Regulations and Directives on IRB Activities

Appendix 3A - Excerpts From 45CFR46A, the "Common Rule"

TITLE 45--PUBLIC WELFARE AND HUMAN SERVICES

PART 46--PROTECTION OF HUMAN SUBJECTS

Subpart A--Basic HHS Policy for Protection of Human Research Subjects

Sec. 46.101 To what does this policy apply?

Authority: 5 U.S.C. 301; 42 U.S.C. 289, 42 U.S.C. 300v-1(b).

Source: 56 FR 28012, 28022, June 18, 1991, unless otherwise noted.

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in Sec. 46.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in Sec. 46.102(e) must be reviewed and approved, in compliance with Sec. 46.101, Sec. 46.102, and Sec. 46.107 through Sec. 46.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy.

[An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the Federal Register or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Protection from Research Risks, Department of Health and Human Services

(HHS), and shall also publish them in the Federal Register or in such other manner as provided in department or agency procedures.

Institutions with HHS-approved assurances on file will abide by provisions of title 45 CFR part 46 subparts A-D. Some of the other Departments and Agencies have incorporated all provisions of title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, subparts B and C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Sec. 46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied: (1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by Sec. 46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by Sec. 46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Sec. 46.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a

cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

Sec. 46.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described is

Sec. 46.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in Sec. 46.103(b)(4) and Sec. 46.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by Sec. 46.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

Sec. 46.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) Public benefit of service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

Appendix 3B, 14CFR1230 Protection Of Human Subjects (NASA)

TITLE 14--AERONAUTICS AND SPACE SPACE ADMINISTRATION

PART 1230--PROTECTION OF HUMAN SUBJECTS--Table of Contents

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Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b).

Source: 56 FR 28012, 28019, June 18, 1991, unless otherwise noted.

Sec. 1230.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate

administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in Sec. 1230.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in Sec. 1230.102(e) must be reviewed and approved, in compliance with Secs. 1230.101, 1230.102, and 1230.107 through 1230.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy.

[An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the Federal Register or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Protection from Research Risks, Department of Health and Human Services (HHS), and shall also publish them in the Federal Register or in such other manner as provided in department or agency procedures. Institutions with HHS-approved assurances on file will abide by provisions of title 45 CFR part 46 subparts A-D. Some of the other Departments and Agencies have incorporated all provisions of title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, subparts B and C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation

of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Sec. 1230.102 Definitions.

(a) Department or agency head means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

(b) Institution means any public or private entity or agency (including federal, state, and other agencies).

(c) Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

(e) Research subject to regulation, and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

- (1) Data through intervention or interaction with the individual, or
- (2) Identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) IRB means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) IRB approval means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) Certification means the official notification by the institution to the supporting department or agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

Sec. 1230.103 Assuring compliance with this policy--research conducted or supported by any Federal Department or Agency.

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, HHS, and approved for federal wide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Protection from Research Risks, HHS.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under Sec. 1230.101 (b) or (i).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and record keeping duties.

(3) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the department or agency head, unless in accord

with Sec. 1230.103(a) of this policy, the existence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, HHS.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under Sec. 1230.101 (b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by Sec. 1230.103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by Sec. 1230.103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

[56 FR 28012, 28019, June 18, 1991; 56 FR 29756, June 28, 1991]

Sec. 1230.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

Sec. 1230.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in Sec. 1230.103(b)(4) and, to the extent required by, Sec. 1230.103(b)(5).

(b) Except when an expedited review procedure is used (see Sec. 1230.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

Sec. 1230.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with Sec. 1230.116. The IRB may require that information, in addition to that specifically mentioned in Sec. 1230.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with Sec. 1230.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

Sec. 1230.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the Federal Register. A copy of the list is available from the Office for Protection from Research Risks, National Institutes of Health, HHS, Bethesda, Maryland 20892.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in Sec. 1230.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

Sec. 1230.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by Sec. 1230.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by Sec. 1230.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Sec. 1230.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

Sec. 1230.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination

of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

Sec. 1230.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

Sec. 1230.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described in Sec. 1230.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in Secs. 1230.103(b)(4) and 1230.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by Sec. 1230.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

Sec. 1230.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the

representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) Public benefit of service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

Sec. 1230.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by Sec. 1230.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by Sec. 1230.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation.

Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

Sec. 1230.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under Sec. 1230.101 (b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the department or agency.

Sec. 1230.119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the department or agency, and final approval given to the proposed change by the department or agency.

Sec. 1230.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

Sec. 1230.122 Use of Federal funds.

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

Sec. 1230.123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has have directed the scientific and technical aspects of an activity has have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

Sec. 1230.124 Conditions.

With respect to any research project or any class of research projects the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

Appendix 3C - Presidential Executive Order 12975

Federal Register: October 5, 1995 (Volume 60, Number 193)
Page 52063-52065
Presidential Documents
Executive Order 12975 of October 3, 1995

PROTECTION OF HUMAN RESEARCH SUBJECTS AND CREATION OF NATIONAL BIOETHICS ADVISORY COMMISSION

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. Review of Policies and Procedures.

(a) Each executive branch department and agency that conducts, supports, or regulates research involving human subjects shall promptly review the protections of the rights and welfare of human research subjects that are afforded by the department's or agency's existing policies and procedures. In conducting this review, departments and agencies shall take account of the recommendations contained in the report of the Advisory Committee on Human Radiation Experiments.

(b) Within 120 days of the date of this order, each department and agency that conducts, supports, or regulates research involving human subjects shall report the results of the review required by paragraph (a) of this section to the National Bioethics Advisory Commission, created pursuant to this order. The report shall include an identification of measures that the department or agency plans or proposes to implement to enhance human subject protections. As set forth in section 5 of this order, the National Bioethics Advisory Commission shall pursue, as its first priority, protection of the rights and welfare of human research subjects.

(c) For purposes of this order, the terms "research" and "human subject" shall have the meaning set forth in the 1991 Federal Policy for the Protection of Human Subjects.

Sec. 2. Research Ethics.

Each executive branch department and agency that conducts, supports, or regulates research involving human subjects shall, to the extent practicable and appropriate, develop professional and public educational programs to enhance activities related to human subjects protection, provide forums for addressing ongoing and emerging issues in human subjects research, and familiarize professionals engaged in nonfederally-funded research with the ethical considerations associated with conducting research involving human subjects. Where appropriate, such professional and educational programs should be organized and conducted with the participation of medical schools, universities, scientific societies, voluntary health organizations, or other interested parties.

Sec. 3. Establishment of National Bioethics Advisory Commission.

- (a) There is hereby established a National Bioethics Advisory Commission ("NBAC"). NBAC shall be composed of not more than 15 members to be appointed by the President. NBAC shall be subject to the Federal Advisory Committee Act, as amended (5 U.S.C. App.).
- (b) The President shall designate a Chairperson from among the members of NBAC.

Sec. 4. Functions.

- (a) NBAC shall provide advice and make recommendations to the National Science and Technology Council and to other appropriate government entities regarding the following matters:
the appropriateness of departmental, agency, or other governmental programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior; and applications, including the clinical applications, of that research.
- (b) NBAC shall identify broad principles to govern the ethical conduct of research, citing specific projects only as illustrations for such principles.
- (c) NBAC shall not be responsible for the review and approval of specific projects.
- (d) In addition to responding to requests for advice and recommendations from the National Science and Technology Council, NBAC also may accept suggestions of issues for consideration from both the Congress and the public. NBAC also may identify other bioethical issues for the purpose of providing advice and recommendations, subject to the approval of the National Science and Technology Council.

Sec. 5. Priorities.

- (a) As a first priority, NBAC shall direct its attention to consideration of: protection of the rights and welfare of human research subjects; and issues in the management and use of genetic information, including but not limited to, human gene patenting.
- (b) NBAC shall consider four criteria in establishing the other priorities for its activities:
the public health or public policy urgency of the bioethical issue;
the relation of the bioethical issue to the goals for Federal investment in science and technology;
the absence of another entity able to deliberate appropriately on the bioethical issue; and the extent of interest in the issue within the Federal Government.

Sec. 6. Administration.

- (a) The heads of executive departments and agencies shall, to the extent permitted by law, provide NBAC with such information as it may require for purposes of carrying out its functions.
- (b) NBAC may conduct inquiries, hold hearings, and establish subcommittees, as necessary. The Assistant to the President for Science and Technology and the Secretary of Health and Human Services shall be notified upon establishment of each subcommittee, and shall be provided information on the name, membership (including chair), function, estimated duration, and estimated frequency of meetings of the subcommittee.
- (c) NBAC is authorized to conduct analyses and develop reports or other materials. In order to augment the expertise present on NBAC, the Secretary of Health and Human Services may contract for the services of nongovernmental consultants who may conduct analyses, prepare reports and background papers, or prepare other materials for consideration by NBAC, as appropriate.

(d) Members of NBAC shall be compensated in accordance with Federal law. Members of NBAC may be allowed travel expenses, including per diem in lieu of subsistence, to the extent permitted by law for persons serving intermittently in the government service (5 U.S.C. 5701-5707).

(e) To the extent permitted by law, and subject to the availability of appropriations, the Department of Health and Human Services shall provide NBAC with such funds as may be necessary for the performance of its functions. The Secretary of Health and Human Services shall provide management and support services to NBAC.

Sec. 7. General Provisions.

(a) Notwithstanding the provisions of any other Executive order, the functions of the President under the Federal Advisory Committee Act that are applicable to NBAC, except that of reporting annually to the Congress, shall be performed by the Secretary of Health and Human Services, in accordance with the guidelines and procedures established by the Administrator of General Services.

(b) NBAC shall terminate two years from the date of this order unless extended prior to that date.

(c) This order is intended only to improve the internal management of the executive branch and it is not intended to create any right, benefit, trust, or responsibility, substantive or procedural, enforceable at law or equity by a party against the United States, its agencies, its officers, or any person.

WILLIAM J. CLINTON
THE WHITE HOUSE,
October 3, 1995.

Appendix 3D - NPD 7100.8C Protection of Human Research Subjects

NASA POLICY DIRECTIVE	Directive:	NPD 7100.8C
	Effective Date:	February 01, 1999
	Expiration Date:	February 01, 2004

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Responsible Office: AM / Chief Health and Medical Officer

Subject: Protection of Human Research Subjects

[Interim Policy Memorandum \(N IPM\) 8900-2, 2/9/99 - 2/9/01](#)

1. POLICY

- a. This NPD sets forth NASA policies for the protection of human research subjects which is primary to the conduct of any human research. All human research conducted or supported by NASA, whether on the ground, in aircraft, or in space, will follow the provisions of NASA regulations contained in 14 CFR Part 1230 and Department of Health and Human Services (HHS) regulations contained in 45 CFR Part 46.
- b. The authorized NASA official for the conduct of human research and the protection of human subjects is the Associate Administrator(AA) for the Office of Life and Microgravity Sciences and Applications (OLMSA). All human research, funded, sponsored, conducted or supported by NASA, will be reviewed by an Institutional Review Board (IRB), approved by NASA or the Office for the Protection from Research Risks (OPRR), HHS. IRB's will be established at NASA Centers to review all ground-based and aeronautical flight research, involving human subjects, that is conducted at the Centers or which utilizes NASA Centers, equipment, or personnel. All research performed on NASA spacecraft, involving crew members, will be reviewed by the IRB at the Johnson Space Center (JSC).
- c. The IRB has authority to approve, disapprove, or require changes in the proposed human research protocols and procedures and to suspend or terminate its approval of research activities that are not conducted in accordance with the approved protocol or that have been associated with serious harm to subjects.
- d. No Principal Investigator (PI) may involve a human being as a subject in research, covered by this Directive, unless the written informed consent of the subject or the subject's legally authorized representative has been obtained. Such consent shall be sought only under circumstances that provide the prospective

subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights or which releases or appears to release the PI, the sponsor, the institution, or its agents from liability for negligence. The conditions under which an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent or under which an IRB may waive the requirements to obtain informed consent, must include all of the following elements which must be documented by the IRB:

- (1) The research involves no more than minimal risk;
- (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- (3) The research could not practicably be carried out without the waiver or alteration;
- (4) Whenever appropriate, the subjects shall be provided with additional pertinent information after participation; and
- (5) Astronaut and other human experimental data derived from or associated with such approved research, must be nonattributable to any individual.

e. All classified human research must have informed consent of the subjects.

f. All institutions proposing human research, funded by NASA, shall be required to give written assurance, as provided in 14 CFR 1230.103, to the authorized NASA official. A Multiple Project Assurance (MPA) on file with the OPRR will satisfy this requirement. Assurances from institutions for projects utilizing NASA facilities, equipment, or personnel will not be accepted; NASA IRB review and approval shall be obtained. NASA Centers conducting human research or studies shall file MPA's with the authorized NASA official every 5 years and provide an annual report on research and IRB activities. NASA Centers, not conducting human research or studies, will file a letter certifying this conclusion with supporting documentation to the authorized NASA official every year.

g. When research covered by this policy takes place in foreign institutions, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. Studies funded or sponsored by NASA must follow this NPD. In these circumstances, if NASA determines that the procedures prescribed by the foreign institution afford protections that are greater to those provided in this policy, the Agency may approve the use of the foreign procedures in addition to the procedural requirements provided in this policy, in accordance with 14 CFR Part 1230.101 (h) and 45 CFR 46.101 (h).

h. PI's are required to familiarize themselves with Agency and Center policies and procedures for the conduct of human research. Any NASA PI or a PI

supported by NASA involved in human research, who does not comply with the policies and procedures of this NPD or does not comply with the protocol as approved, may have his or her research immediately suspended or terminated when such noncompliance becomes known to the appropriate IRB, NASA Center Director, or AA of OLMSA. Evidence of noncompliance may be cause for the application of sanctions by any of these officials.

2. APPLICABILITY

a. This NPD applies to NASA Headquarters and all NASA Centers, including Component Facilities, and will be followed by all members of the research teams in all research experiments involving human subjects that are funded or sponsored by NASA or conducted in NASA facilities, aircraft, or spacecraft.

All human research conducted under a cooperative or reimbursable arrangement or agreement entered into by NASA and another Government agency, private entity, non-Federal public entity, or foreign entity must also comply with the terms and conditions of this NPD.

b. Research activities involving the collection or study of existing data, documents, records, pathological or diagnostic specimens are exempted from this NPD, if these sources are publicly available, or if its information is recorded in such a manner that subjects cannot be identified, directly or through identifier links to the subjects.

3. AUTHORITY

a. 42 U.S.C. 2473 (c)(1), Section 203 (c)(1), The National Aeronautics and Space Act of 1958, as amended

b. 14 CFR Part 1230 and 45 CFR Part 46, "Protection of Human Subjects"

4. REFERENCES

a. World Medical Association Declaration of Helsinki adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Assembly, Tokyo, Japan, October 1975; 35th World Medical Assembly, Venice, Italy, October 1983; and the 41st World Medical Assembly, Hong Kong, September 1989.

5. RESPONSIBILITY

a. The authorized NASA official for the protection of human subjects is the AA of OLMSA, NASA Headquarters, who is empowered, subject to conditions and limitations imposed by immediate superiors, to authorize human research. The authorized NASA official is responsible for ensuring that the written institutional

assurances related to NASA-supported human research, NASA Center MPA's, and any NASA Center letters certifying that human research or studies not being conducted at the Center, are filed in a timely manner with NASA Headquarters. All or part of the authority may be redelegated, without power of further redelegation, to a senior NASA Headquarters employee, usually the OLMSA Deputy AA, who reports to the authorized NASA official.

b. The authorized NASA official is responsible for ensuring that the Administrator; the Chief Medical Officer, OLMSA; the AA, Office of Safety and Mission Assurance; the NASA General Counsel; the AA, Office of Aero-Space Technology (when appropriate); and the NASA Inspector General (when appropriate) are kept fully and currently informed, through official channels, of significant actions, problems, or other matters of substance related to the exercise of this authority.

c. The NASA Center Directors are responsible for implementing this NPD within their assigned areas of responsibility. The Center Directors are responsible for ensuring that the written institutional assurances related to Center-supported human research, Center MPA's, and any NASA Center letters certifying that human research or studies not being conducted at the Center are filed in a timely manner with the authorized NASA official. In addition, the Center Directors are responsible for establishing an IRB at their Centers to review all ground-based, aeronautical, and aerospace flight research involving human subjects that is conducted at their Center.

d. All research involving human subjects, including flight crews, which is performed in NASA spacecraft will be reviewed by the IRB at the JSC.

e. The primary responsibility of the IRB is to protect the rights of and ensure the safety of every person who is a subject of any research in NASA facilities, including NASA aircraft or spacecraft, or is a subject of NASA-funded or NASA-sponsored research. Specifically, the IRB's are responsible for the following:

(1) Approving, disapproving, or requiring changes in the proposed human research protocols and procedures;

(2) Ensuring that the human subjects have given informed consent and reviewing such informed consent, or documenting the reasons and safeguards in all cases where the informed consent procedure, or any element of such procedure, has been altered or waived; and

(3) Suspending or terminating approval of research activities that are not being conducted in accordance with the approved protocol or that have been associated with serious harm to subjects.

f. All PI's are responsible for complying with Agency and Center policies and procedures for the conduct of human research.

6. DELEGATION OF AUTHORITY

None.

7. MEASUREMENTS

Measures of Agency compliance with this Directive for the protection of human subjects in NASA research are contained in Attachment A.

8. CANCELLATION

NMI 7100.8B dated August 3, 1995

/s/ Daniel S. Goldin
Administrator

ATTACHMENT A: (TEXT)

Metrics or measures of Agency compliance with this Directive for the protection of human subjects in NASA research are the following:

Percent of NASA Centers with active MPA and certifying letters on file with the Authorized NASA Official.

Percent of NASA Centers filing timely MPA's or certifying letters.
Number of research proposals reviewed by IRB's.

Number of research proposals approved by IRB's.

Number of complaints to IRB's.

Timeliness of response to complaints including Headquarters notifications.

Number and type of sanctions imposed.

Number of audits conducted and corrective measures adopted.

(URL for Graphic)

None .

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Appendix 3E - NASA 10HERD Record System

Extract from Federal Register: January 28, 1998 (Volume 63, Number 18)
Original at <http://198.17.75.65/fril/1998/19980128/98-2055.txt>
Page 4290-4306 DOCID:fr28ja98-122

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
[Notice 98-007]
Privacy Act; Annual Notice and Amendment to Systems of Records
AGENCY: National Aeronautics and Space Administration (NASA).
ACTION: Annual Notice and Amendment of Systems of Records.

NASA 10HERD

SYSTEM NAME:

Human Experimental and Research Data Records.

SECURITY CLASSIFICATION:

None.

SYSTEM LOCATION:

Locations 2, 3, 5, 6, and 9, as stated in Appendix A.

CATEGORIES OF INDIVIDUALS COVERED BY THE SYSTEM:

Individuals who have been involved in space flight, aeronautical research flight, and/or participated in NASA tests or experimental or research programs; Civil Service employees, military, employees of other Government agencies, contractor employees, students, human subjects (volunteer or paid), and other volunteers on whom information is collected as part of an experiment or study.

CATEGORIES OF RECORDS IN THE SYSTEM:

Data obtained in the course of an experiment, test, or research medical data from inflight records, other information collected in connection with an experiment, text, or research.

AUTHORITY FOR MAINTENANCE OF THE SYSTEM:

42 U.S.C. 2475 and 44 U.S.C. 3101.

ROUTINE USES OF RECORDS MAINTAINED IN THE SYSTEM,
INCLUDING CATEGORIES OF USERS AND THE PURPOSE OF SUCH USES:

The information contained in this system of records is used by NASA for the purposes of evaluating new analytical techniques, equipment, and re-examining flight data for alternative interpretations, developing applications of experimental techniques or equipment, reviewing and improving operational procedures with respect to experimental protocols (both inflight and ground), life support system operating procedures, determining human engineering requirements, and carrying out other research.

In addition to the internal use of the information contained in this system of records, the following are routine uses outside of NASA: Disclosures to other individuals or organizations, including Federal, State, or local agencies, and nonprofit, educational, or private entities, who are participating in NASA programs or are otherwise furthering the understanding or application of biological, physiological, and behavioral phenomena as reflected in the data contained in this system of records; and the standard routine use 4 as set forth in Appendix B.

POLICIES AND PRACTICES FOR STORING, RETRIEVING, ACCESSING, RETAINING, AND DISPOSING OF RECORDS IN THE SYSTEM: STORAGE:

Paper of hard-copy documents, electronic media, micrographic media, photographs, or motion pictures film; and various medical recordings, such as, electrocardiograph tapes, stripcharts, and x-rays.

RETRIEVABILITY:

By name, experiment, or test; arbitrary experimental subject number; flight designation; or crew member designation on a particular space or aeronautical flight.

SAFEGUARDS:

Access is limited to Government personnel requiring access in the discharge of their duties, and to appropriate support contractor employees on a need-to-know basis. Computerized records are identified by code number and records are maintained in locked rooms or files. Records are protected in accordance with the requirements and procedures which appear in the NASA regulations set forth in 14 CFR part 1212.

RETENTION AND DISPOSAL:

Records are maintained in accordance with NASA Records Retention Schedules, Schedule 7.

SYSTEM MANAGER(S) AND ADDRESS:

Director, Occupational Health Office, Location 1.

Subsystem Managers: Chief Engineer, Location 2; Director of Man/Systems Integration Division, Location 3; Assistant Director for Life Sciences, Space and Life Sciences Directorate, Location 5; Director, Biomedical Operations Office, Location 6; Director, Management Services Office, Location 9. Locations are as set forth in Appendix A.

NOTIFICATION PROCEDURE:

Information may be obtained from the system or subsystem manager named above.

RECORD ACCESS PROCEDURES:

Requests from individuals should be addressed to the same address as stated in the Notification Section above.

CONTESTING RECORD PROCEDURES:

The NASA regulations for access to records and for contesting and appealing initial determinations by the individual concerned appear at 14 CFR part 1212.

RECORD SOURCE CATEGORIES:

Experimental test subjects, physicians, principal investigators and other researchers, and previous experimental test or research records.

Appendix 3F - Charter of the KSC IRB

HumanRes
Rev. Basic

KSC Councils, Boards, & Working Groups Charter

Name	KSC HUMAN RESEARCH INSTITUTIONAL REVIEW BOARD (IRB)
Charter	<ul style="list-style-type: none"> • Review and approve/disapprove any KSC proposals involving human research. • Ensure the health, safety, and ethical treatment of all human subjects involved in human research at KSC. This includes, but is not limited to, reviewing and ensuring informed consent, assuring adequate safeguards are in place, and evaluating the risk vs. benefit of the human research. • Review and investigate any incidents that occur (both to equipment and subjects) as a result of research at KSC. • Suspend or terminate approval of research activities that are not being conducted in accordance with the approved protocol or that have been associated with significant harm to subjects. • Perform regular periodic review of ongoing KSC research done by reviewing reports from investigators (at least annual) regarding the status of their research project. <p>These activities include studies done outside of KSC but using KSC funds.</p>
Membership	<p>Chair: Chief, Aerospace Medicine and Occupational Health Branch Co-Chair/Secretary: Medical Officer, Aerospace Medicine and Occupational Health Branch Recorder: Co-Chair/Secretary as above Members: Representatives from BA, CC, QA, TA, YA, an outside technical expert as appointed by the Center Director Facilitator: Not Required</p>
Period of Performance	<p>Start date: October 21, 1980 End date: Indefinite</p>
Deliverables	<p>Bi-annual status report to the Safety & Health Council (SHC) identifying:</p> <ol style="list-style-type: none"> a. Major accomplishments b. Major problems identified and status <p>Annual status report to NASA HQ:</p> <ol style="list-style-type: none"> c. Summary of proposals reviewed b. Summary of any incidents that occurred to test subjects and corrective actions implemented c. Summary of any actions taken against a Principal Investigator or a proposal
Meeting Guidelines	<ol style="list-style-type: none"> 1. Meeting Frequency: As needed, at least once annually 2. Length of Appointment: Indefinite 3. Minutes/Agenda Requirements: Research proposals as developed by Principal Investigators. 4. The individual votes of each member concerning each research

	<p>proposal will be recorded.</p> <p>5. Minutes to be posted in Business World and given to the SHC Secretary. An electronic copy of the minutes to be provided to the Continuous Improvement (CI) Specialist. KSC Chief Safety Officer to be notified of all meetings.</p>
Reporting To	<p><u>original signed by</u> _____ <u>12/07/01</u> J. Chris Fairey, Director of Spaceport Services Date</p>
KSC Roadmap Objective and/or Strategy	<p>Guiding Principle: Safety and Health First Objective 4.2: Strengthen KSC's safety, health, security & environmental stewardship.</p>
KDP Reference	<p>NPD 7100.8C, Protection of Human Research Subjects KDP-P-2560A, Human Research Ethical Review KDP-B-1036, BOA for Spaceport Services</p>

KSC Human Research IRB Charter Concurrence Sheet:

original signed by 01/16/02
James L. Jennings Date
Deputy Director (AA-A)

original signed by
Michael E. Wetmore for 12/10/01
David A. King Date
Director of Shuttle Processing (PH)

original signed by 02/28/02
Kenny E. Aguilar Date
Director, Equal Opportunity (AJ)

original signed by 01/03/02
J. Chris Fairey Date
Director of Spaceport Services (TA)

original signed by 03/22/02
Richard E. Arbuthnot Date
Director, Workforce & Diversity
Management (BA)

original signed by 12/07/01
John J. Talone Date
Director of International Space Station &
Payloads Processing (UB)

original signed by
Tracey Lee Crittenden for 12/10/01
Bruce H. S. Anderson Date
Chief Counsel (CC)

original signed by
Robert R. Heuser for 12/07/01
Stephen M. Francois Date
Manager of ELV & Payload Carriers
Program (VA)

original signed by 12/12/01
N. A. Carroll Date
Chief Financial Officer (GG)

original signed by 01/22/02
JoAnn H. Morgan Date
Director of External Relations &
Business Development (XA)

original signed by 01/11/02
Ramon Lugo Date
Director, Joint Performance Management
Office (JP)

original signed by 12/17/01
James R. Heald Date
Director of Spaceport Engineering
Technology (YA)

original signed by 01/17/02
Colonel James D. Halsell, Jr. Date
Manager, Launch Integration (MK)

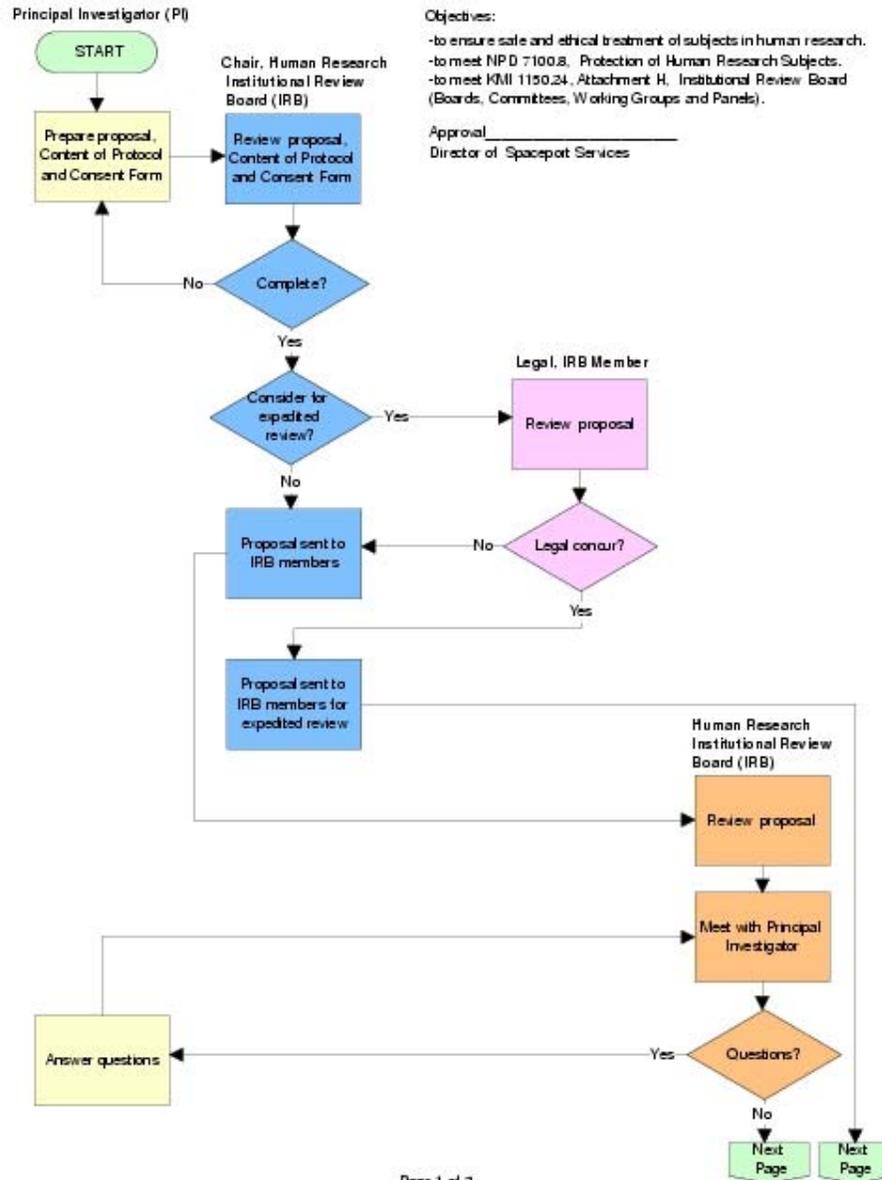
original signed by 12/07/01
James Hattaway, Jr. Date
Director, Procurement Office (OP)

original signed by
Ann Montgomery for 12/04/01
Shannon D. Bartell Date
Director of Safety, Health, & Independent
Assessment (QA)

Appendix 3G

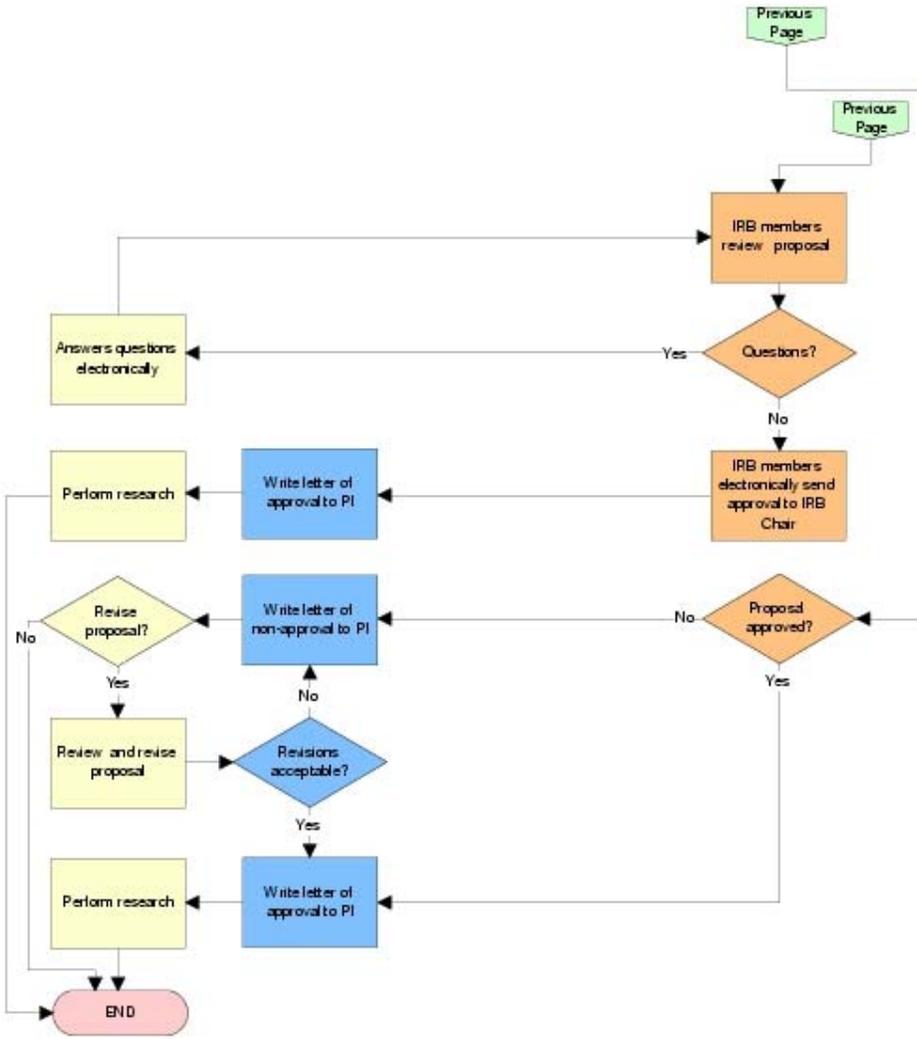
Human Research Ethical Review

KDP-P-2500
REV. A



RELEASED - Printed documents may be obsolete; validate prior to use.

KDP-P-2500
Rev. A



RELEASED - Printed documents may be obsolete; validate prior to use.

Appendix 4 - Evaluation of Risk

Appendix 4A - Examples of Procedures Imposing Minimal Risk

(from JSC 20483B)

1. Collection of hair and nail clippings, in a non-disfiguring manner; deciduous teeth, and permanent teeth if patient care indicates a need for extraction.
2. Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.
3. Recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject, or an invasion of the subject's privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echosonography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays, microwaves).
4. Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an 8-week period and no more than two venipunctures per week, from subjects 18 years of age or older and who are in good health and not pregnant.
5. Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth, and the process is accomplished in accordance with accepted prophylactic techniques.
6. Voice recordings made for research purposes such as investigations of speech defects.
7. Moderate exercise by healthy volunteers.
8. The study of existing data, documents, records, pathological specimens, or diagnostic specimens.
9. Research on individual or group behavior or characteristics of individuals, such as studies of perception, cognition, game theory, or test development, where the investigator does not manipulate subjects' behavior and the research will not involve stress to subjects.
10. Research on drugs or devices for which an investigational exemption is not required.

Appendix 4B - Investigational Device Risk Determination

[U.S. Food and Drug Administration - Center for Devices and Radiological Health]

SIGNIFICANT RISK AND NONSIGNIFICANT RISK MEDICAL DEVICE STUDIES

(FDA Information Sheets October 1, 1995; This replaces Bluebook Memorandum IDE Memorandum D86-1 (July 25, 1986) with the same title)

The Investigational Device Exemption (IDE) regulations (21 CFR Part 812) describe two types of device studies, "significant risk" (SR) and "nonsignificant risk" (NSR). An SR device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. An NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations (21 CFR Part 56) to identify certain studies that may be approved through an "expedited review" procedure. For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study (21 CFR Part 50).

Distinguishing Between SR and NSR Device Studies

The effect of the SR/NSR decision is very important to research sponsors and investigators. SR device studies are governed by the IDE regulations (21 CFR Part 812). NSR device studies have fewer regulatory controls than SR studies and are governed by the abbreviated requirements [21 CFR 812.2(b)]. The major differences are in the approval process and in the record keeping and reporting requirements. The SR/NSR decision is also important to FDA because the IRB serves, in a sense, as the FDA's surrogate with respect to review and approval of NSR studies. FDA is usually not apprised of the existence of approved NSR studies because sponsors and IRBs are not required to report NSR device study approvals to FDA.

If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA. If an IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approve the investigation. To help in the determination of the risk status of the device, IRBs should review

information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination [21 CFR 812.150(b)(10)].

SR/NSR Studies and the IRB

The NSR/SR Decision

The assessment of whether or not a device study presents a NSR is initially made by the sponsor. If the sponsor considers that a study is NSR, the sponsor provides the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The IRB may ask the sponsor for information such as a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The IRB should ask the sponsor whether other IRBs have reviewed the proposed study and what determination was made. The sponsor should inform the IRB of the FDA's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor must notify FDA that a SR determination has been made. The study can be conducted at that institution as a SR investigation following FDA approval of an IDE application.

The risk determination should be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses a SR, an IRB must consider the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure should be considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device. Two examples follow:

- * The study of a pacemaker that is a modification of a commercially-available pacemaker poses a SR because the use of any pacemaker presents a potential for serious harm to the subjects. This is true even though the modified pacemaker may pose less risk, or only slightly greater risk, in comparison to the commercially-available model. The amount of potential reduced or increased risk associated

with the investigational pacemaker should only be considered (in relation to possible decreased or increased benefits) when assessing whether the study can be approved.

* The study of an extended wear contact lens is considered SR because wearing the lens continuously overnight while sleeping presents a potential for injuries not normally seen with daily wear lenses, which are considered NSR.

FDA has the ultimate decision in determining if a device study is SR or NSR. If the FDA does not agree with an IRB's decision that a device study presents an NSR, an IDE application must be submitted to FDA. On the other hand, if a sponsor files an IDE with FDA because it is presumed to be an SR study, but FDA classifies the device study as NSR, the FDA will return the IDE application to the sponsor and the study would be presented to IRBs as an NSR investigation.

IRB and Sponsor Responsibilities Following SR/NSR Determination

If IRB decides the study is Significant Risk:

1. IRB Responsibilities:

- o Notify sponsor and investigator of SR decision
- o After IDE obtained by sponsor, proceed to review study applying requisite criteria (21 CFR 56.111)

2. Sponsor Responsibilities:

- o Submit IDE to FDA or, if electing not to proceed with study, notify FDA (CDRH Program Operations Staff 301-594-1190) of the SR determination;
- o Study may not begin until FDA approves IDE and IRB approves the study.
- o Sponsor and investigator(s) must comply with IDE regulations (21 CFR Part 812), as well as informed consent and IRB regulations (21 CFR Parts 50 and 56).

If the IRB decides the study is Nonsignificant Risk:

1. IRB proceeds to review study applying requisite criteria (21 CFR 56.111)
2. If the study is approved by the IRB, the sponsor and investigator must comply with "abbreviated IDE requirements" [21 CFR 812.2(b)], and the Informed Consent and IRB regulations (21 CFR Parts 50 and 56).

The Decision to Approve or Disapprove

Once the SR/NSR decision has been reached, the IRB should consider whether

the study should be approved or not. The criteria for deciding if SR and NSR studies should be approved are the same as for any other FDA regulated study (21 CFR 56.111). The IRB should assure that risks to subjects are minimized and are reasonable in relation to anticipated benefits and knowledge to be gained, subject selection is equitable, informed consent materials and procedures are adequate, and provisions for monitoring the study and protecting the privacy of subjects are acceptable. To assure that the risks to the subject are reasonable in relation to the anticipated benefits, the risks and benefits of the investigation should be compared to the risks and benefits of alternative devices or procedures. This differs from the judgment about whether a study poses a SR or NSR which is based solely upon the seriousness of the harm that may result from the use of the device. Minutes of IRB meetings must document the rationale for SR/NSR and subsequent approval or disapproval decisions for the clinical investigation.

FDA considers studies of all significant risk devices to present more than minimal risk; thus, full IRB review for all studies involving significant risk devices is necessary. Generally, IRB review at a convened meeting is also required when reviewing NSR studies. Some NSR studies, however, may qualify as minimal risk [21 CFR 56.102(i)] and the IRB may choose to review those studies under its expedited review procedures (21 CFR 56.110).

Examples of NSR/SR Devices

The following examples are provided to assist sponsors and IRBs in making SR/NSR determinations. The list includes many commonly used medical devices. Inclusion of a device in the NSR category should not be viewed as a conclusive determination, because the proposed use of a device in a study is the ultimate determinant of the potential risk to subjects. It is unlikely that a device included in the SR category could be deemed NSR due to the inherent risks associated with most such devices.

NONSIGNIFICANT RISK DEVICES

- * Low Power Lasers for treatment of pain (Note: an IDE is required when safety and effectiveness data are collected which will be submitted in support of a marketing application.)
- * Caries Removal Solution
- * Daily Wear Contact Lenses and Associated Lens Care Products not intended for use directly in the eye (e.g., cleaners; disinfecting, rinsing and storage solutions)
- * Contact Lens Solutions intended for use directly in the eye (e.g., lubricating/rewetting solutions) using active ingredients or preservation systems with a history of prior ophthalmic/contact lens use or generally recognized as safe for ophthalmic use
- * Conventional Gastroenterology and Urology Endoscopes and/or Accessories
- * Conventional Laparoscopes, Culdoscopes, and Hysteroscopes
- * Dental Filling Materials, Cushions or Pads made from traditional

materials and designs

- * Denture Repair Kits and Realigners
- * Digital Mammography (Note: an IDE is required when safety and effectiveness data are collected which will be submitted in support of a marketing application.)
- * Electroencephalography (e.g., new recording and analysis methods, enhanced diagnostic capabilities)
- * Externally Worn Monitors for Insulin Reactions
- * Functional Electrical Neuromuscular Stimulators
- * General Biliary Catheters
- * General Urological Catheters (e.g., Foley and diagnostic catheters)
- * Jaundice Monitors for Infants
- * Magnetic Resonance Imaging (MRI) Devices within FDA specified parameters
- * Menstrual Pads (Cotton or Rayon only)
- * Menstrual Tampons (Cotton or Rayon only)
- * Nonimplantable Electrical Incontinence Devices
- * Nonimplantable Male Reproductive Aids with no components that enter the vagina
- * Ob/Gyn Diagnostic Ultrasound within FDA approved parameters
- * Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain
- * Wound Dressings, excluding absorbable hemostatic devices and dressings (also excluding Interactive Wound and Burn Dressings)

SIGNIFICANT RISK DEVICES

GENERAL MEDICAL USE

- * Catheters:
 - o Urology - urologic with anti-infective coatings
 - o General Hospital - long-term percutaneous, implanted, subcutaneous and intravascular
 - o Neurological - cerebrovascular, occlusion balloon
 - o Cardiology - transluminal coronary angioplasty, intra-aortic balloon with control system
- * Collagen Implant Material for use in ear, nose and throat, orthopedics, plastic surgery, urological and dental applications
- * Surgical Lasers for use in various medical specialties
- * Tissue Adhesives for use in neurosurgery, gastroenterology, ophthalmology, general and plastic surgery, and cardiology

ANESTHESIOLOGY

- * Breathing Gas Mixers
- * Bronchial Tubes
- * Electroanesthesia Apparatus
- * Epidural and Spinal Catheters
- * Epidural and Spinal Needles
- * Esophageal Obturators

- * Gas Machines for anesthesia or analgesia
- * High Frequency Jet Ventilators greater than 150 BPM
- * Rebreathing Devices
- * Respiratory Ventilators
- * Tracheal Tubes

CARDIOVASCULAR

- * Aortic and Mitral Valvoplasty Catheters
- * Arterial Embolization Devices
- * Cardiac Assist Devices: artificial heart (permanent implant and short term use), cardiomyoplasty devices, intra-aortic balloon pumps, ventricular assist devices
- * Cardiac Bypass Devices: oxygenators, cardiopulmonary non-roller blood pumps, closed chest devices
- * Cardiac Pacemaker/Pulse Generators: antitachycardia, esophageal, external transcutaneous, implantable
- * Cardiopulmonary Resuscitation (CPR) Devices
- * Cardiovascular/Intravascular Filters
- * Coronary Artery Retroperfusion Systems
- * Coronary Occluders for ductus arteriosus, atrial and septal defects
- * Coronary and Peripheral Arthrectomy Devices
- * Extracorporeal Membrane Oxygenators (ECMO)
- * Implantable Cardioverters/Defibrillators
- * Laser Coronary and Peripheral Angioplasty Devices
- * Myoplasty Laser Catheters
- * Organ Storage/Transport Units
- * Pacing Leads
- * Percutaneous Conduction Tissue Ablation Electrodes
- * Peripheral, Coronary, Pulmonary, Renal, Vena Caval and Peripheral Stents
- * Replacement Heart Valves
- * RF Catheter Ablation and Mapping Systems
- * Ultrasonic Angioplasty Catheters
- * Vascular and Arterial Graft Prostheses
- * Vascular Hemostasis Devices

DENTAL

- * Absorbable Materials to aid in the healing of periodontal defects and other maxillofacial applications
- * Bone Morphogenic Proteins with and without bone, e.g., Hydroxyapatite (HA)
- * Dental Lasers for hard tissue applications
- * Endosseous Implants and associated bone filling and augmentation materials used in conjunction with the implants
- * Subperiosteal Implants
- * Temporomandibular Joint (TMJ) Prostheses

EAR, NOSE AND THROAT

- * Auditory Brainstem Implants
- * Cochlear Implants
- * Laryngeal Implants
- * Total Ossicular Prosthesis Replacements

GASTROENTEROLOGY AND UROLOGY

- * Anastomosis Devices
- * Balloon Dilation Catheters for benign prostatic hyperplasia (BPH)
- * Biliary Stints
- * Components of Water Treatment Systems for Hemodialysis
- * Dialysis Delivery Systems
- * Electrical Stimulation Devices for sperm collection
- * Embolization Devices for general urological use
- * Extracorporeal Circulation Systems
- * Extracorporeal Hyperthermia Systems
- * Extracorporeal Photopheresis Systems
- * Femoral, Jugular and Subclavian Catheters
- * Hemodialyzers
- * Hemofilters
- * Implantable Electrical Urinary Incontinence Systems
- * Implantable Penile Prostheses
- * Injectable Bulking Agents for incontinence
- * Lithotripters (e.g., electrohydraulic extracorporeal shock-wave, laser, powered mechanical, ultrasonic)
- * Mechanical/Hydraulic Urinary Incontinence Devices
- * Penetrating External Penile Rigidity Devices with components that enter the vagina
- * Peritoneal Dialysis Devices
- * Peritoneal Shunt
- * Plasmapheresis Systems
- * Prostatic Hyperthermia Devices
- * Urethral Occlusion Devices
- * Urethral Sphincter Prostheses
- * Urological Stints (e.g., ureteral, prostate)

GENERAL AND PLASTIC SURGERY

- * Absorbable Adhesion Barrier Devices
- * Absorbable Hemostatic Agents
- * Artificial Skin and Interactive Wound and Burn Dressings
- * Injectable Collagen
- * Implantable Craniofacial Prostheses
- * Repeat Access Devices for surgical procedures
- * Sutures

GENERAL HOSPITAL

- * Implantable Vascular Access Devices

- * Infusion Pumps (implantable and closed-loop - depending on the infused drug)

NEUROLOGICAL

- * Electroconvulsive Therapy (ECT) Devices
- * Hydrocephalus Shunts
- * Implanted Intracerebral/Subcortical Stimulators
- * Implanted Intracranial Pressure Monitors
- * Implanted Spinal Cord and Nerve Stimulators and Electrodes

OBSTETRICS AND GYNECOLOGY

- * Antepartum Home Monitors for Non-Stress Tests
- * Antepartum Home Uterine Activity Monitors
- * Catheters for Chorionic Villus Sampling (CVS)
- * Catheters Introduced into the Fallopian Tubes
- * Cervical Dilation Devices
- * Contraceptive Devices:
 - o Cervical Caps
 - o Condoms (for men) made from new materials (e.g., polyurethane)
 - o Contraceptive In Vitro Diagnostics (IVDs)
 - o Diaphragms
 - o Female Condoms
 - o Intrauterine Devices (IUDs)
 - o New Electrosurgical Instruments for Tubal Coagulation
 - o New Devices for Occlusion of the Vas Deferens
 - o Sponges
 - o Tubal Occlusion Devices (Bands or Clips)
- * Devices to Prevent Post-op Pelvic Adhesions
- * Embryoscopes and Devices intended for fetal surgery
- * Falloposcopes and Falloposcopic Delivery Systems
- * Intrapartum Fetal Monitors using new physiological markers
- * New Devices to Facilitate Assisted Vaginal Delivery
- * Thermal Systems for Endometrial Ablation

OPHTHALMICS

- * Class III Ophthalmic Lasers
- * Contact Lens Solutions intended for direct instillation (e.g., lubrication/rewetting solutions) in the eye using new active agents or preservatives with no history of prior ophthalmic/contact lens use or not generally recognized as safe for ophthalmic use
- * Corneal Implants
- * Corneal Storage Media
- * Epikeratophakia Lenticulas
- * Extended Wear Contact Lens
- * Eye Valve Implants (glaucoma implant)
- * Intraocular Lenses (IOLs) [21 CFR part 813]
- * Keratoprostheses

- * Retinal Reattachment Systems: fluids, gases, perfluorocarbons, perfluoropropane, silicone oil, sulfur hexafluoride, tacks
- * Viscosurgical Fluids

ORTHOPEDICS AND RESTORATIVE

- * Bone Growth Stimulators
- * Calcium Tri-Phosphate Hydroxyapatite Ceramics
- * Collagen and Bone Morphogenic Protein Meniscus Replacements
- * Implantable Prostheses (ligament, tendon, hip, knee, finger)

RADIOLOGY

- * Boron Neutron Capture Therapy
- * Hyperthermia Systems and Applicators
- * Image Guided Surgery

Your comments and suggestions for additional examples are welcome and should be sent to:

Program Operation Staffs (HFZ-403)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850

Appendix 5 – FDA Approval of Drugs and Devices

Appendix 5A - Investigational New Drug Code and Application

[Code of Federal Regulations]
[Title 21, Volume 5]
[Revised as of April 1, 2001]
From the U.S. Government Printing Office via GPO Access
[CITE: 21CFR312]

[Page 57-95]

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--

Continued

PART 312--INVESTIGATIONAL NEW DRUG APPLICATION

Subpart A--General Provisions

Sec.

- 312.1 Scope.
- 312.2 Applicability.
- 312.3 Definitions and interpretations.
- 312.6 Labeling of an investigational new drug.
- 312.7 Promotion and charging for investigational drugs.
- 312.10 Waivers.

Subpart B--Investigational New Drug Application (IND)

- 312.20 Requirement for an IND.
- 312.21 Phases of an investigation.
- 312.22 General principles of the IND submission.
- 312.23 IND content and format.
- 312.30 Protocol amendments.
- 312.31 Information amendments.
- 312.32 IND safety reports.
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Subpart A--General Provisions

Sec. 312.1 Scope.

(a) This part contains procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND's). An investigational new drug for which an IND is in effect in accordance with this part is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.

(b) References in this part to regulations in the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

Sec. 312.2 Applicability.

(a) Applicability. Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)).

(b) Exemptions. (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of Sec. 312.7.

(2)(i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if (a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (b) it is shipped in compliance with Sec. 312.160.

(ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part: (a) blood grouping serum; (b) reagent red blood cells; and (c) anti-human globulin.

(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped

in accordance with Sec. 312.160.

(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.

(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

(6) A clinical investigation involving an exception from informed consent under Sec. 50.24 of this chapter is not exempt from the requirements of this part.

(c) Bioavailability studies. The applicability of this part to in vivo bioavailability studies in humans is subject to the provisions of Sec. 320.31.

(d) Unlabeled indication. This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.

(e) Guidance. FDA may, on its own initiative, issue guidance on the applicability of this part to particular investigational uses of drugs. On request, FDA will advise on the applicability of this part to a planned clinical investigation.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51529, Oct. 2, 1996; 64 FR 401, Jan. 5, 1999]

Sec. 312.3 Definitions and interpretations.

(a) The definitions and interpretations of terms contained in section 201 of the Act apply to those terms when used in this part:

(b) The following definitions of terms also apply to this part:

Act means the Federal Food, Drug, and Cosmetic Act (secs. 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301-392)).

Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

Contract research organization means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

FDA means the Food and Drug Administration.

IND means an investigational new drug application. For purposes of this part, "IND" is synonymous with "Notice of Claimed Investigational Exemption for a New Drug."

Investigational new drug means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.

Investigator means an individual who actually conducts a clinical

investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.

Marketing application means an application for a new drug submitted under section 505(b) of the act or a biologics license application for a biological product submitted under the Public Health Service Act.

Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

Subject means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

[52 FR 8831, Mar. 19, 1987, as amended at 64 FR 401, Jan. 5, 1999; 64 FR 56449, Oct. 20, 1999]

Sec. 312.22 General principles of the IND submission.

(a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

(b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

(c) The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human

studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND should serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year.

(d) The IND format set forth in Sec. 312.23 should be followed routinely by sponsors in the interest of fostering an efficient review of applications. Sponsors are expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information. Section 312.23 outlines the information needed for a commercially sponsored IND for a new molecular entity. A sponsor-investigator who uses, as a research tool, an investigational new drug that is already subject to a manufacturer's IND or marketing application should follow the same general format, but ordinarily may, if authorized by the manufacturer, refer to the manufacturer's IND or marketing application in providing the technical information supporting the proposed clinical investigation. A sponsor-investigator who uses an investigational drug not subject to a manufacturer's IND or marketing application is ordinarily required to submit all technical information supporting the IND, unless such information may be referenced from the scientific literature.

Sec. 312.23 IND content and format.

(a) A sponsor who intends to conduct a clinical investigation subject to this part shall submit an "Investigational New Drug Application" (IND) including, in the following order:

(1) Cover sheet (Form FDA-1571). A cover sheet for the application containing the following:

(i) The name, address, and telephone number of the sponsor, the date of the application, and the name of the investigational new drug.

(ii) Identification of the phase or phases of the clinical investigation to be conducted.

(iii) A commitment not to begin clinical investigations until an IND covering the investigations is in effect.

(iv) A commitment that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation and that the investigator will report to the IRB proposed changes in the research activity in accordance with the requirements of part 56.

(v) A commitment to conduct the investigation in accordance with all other applicable regulatory requirements.

(vi) The name and title of the person responsible for monitoring the conduct and progress of the clinical investigations.

(vii) The name(s) and title(s) of the person(s) responsible under

Sec. 312.32 for review and evaluation of information relevant to the safety of the drug.

(viii) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer--in lieu of a listing of the specific obligations transferred--may be submitted.

(ix) The signature of the sponsor or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the United States, the IND is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(2) A table of contents.

(3) Introductory statement and general investigational plan. (i) A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug (if known), the formulation of the dosage form(s) to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).

(ii) A brief summary of previous human experience with the drug, with reference to other IND's if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s).

(iii) If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal.

(iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (a) The rationale for the drug or the research study; (b) the indication(s) to be studied; (c) the general approach to be followed in evaluating the drug; (d) the kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate); (e) the estimated number of patients to be given the drug in those studies; and (f) any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

(4) [Reserved]

(5) Investigator's brochure. If required under Sec. 312.55, a copy of the investigator's brochure, containing the following information:

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

(iv) A summary of information relating to safety and effectiveness

in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

(6) Protocols. (i) A protocol for each planned study. (Protocols for studies not submitted initially in the IND should be submitted in accordance with Sec. 312.30(a).) In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation--an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose--and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report.

(ii) In Phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of nonresponders to an alternative therapy.

(iii) A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

(a) A statement of the objectives and purpose of the study.

(b) The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

(c) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

(d) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

(e) The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

(f) A description of the observations and measurements to be made to fulfill the objectives of the study.

(g) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

(7) Chemistry, manufacturing, and control information. (i) As appropriate for the particular investigations covered by the IND, a section describing the composition, manufacture, and control of the drug substance and the drug product. Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

(ii) It should be emphasized that the amount of information to be submitted depends upon the scope of the proposed clinical investigation.

For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

(iii) As drug development proceeds and as the scale or production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger-scale production needed for expanded clinical trials, the sponsor should submit information amendments to supplement the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

(iv) Reflecting the distinctions described in this paragraph (a)(7), and based on the phase(s) to be studied, the submission is required to contain the following:

(a) Drug substance. A description of the drug substance, including its physical, chemical, or biological characteristics; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance; and information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies. Reference to the current edition of the United States Pharmacopeia--National Formulary may satisfy relevant requirements in this paragraph.

(b) Drug product. A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable

variations that may be expected during the investigational stage; the name and address of the drug product manufacturer; a brief general description of the manufacturing and packaging procedure as appropriate for the product; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product; and information sufficient to assure the product's stability during the planned clinical studies.

Reference to the current edition of the United States Pharmacopeia--National Formulary may satisfy certain requirements in this paragraph.

(c) A brief general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial.

(d) Labeling. A copy of all labels and labeling to be provided to each investigator.

(e) Environmental analysis requirements. A claim for categorical exclusion under Sec. 25.30 or 25.31 or an environmental assessment under Sec. 25.40.

(8) Pharmacology and toxicology information. Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations. Guidance documents are available from FDA that describe ways in which these requirements may be met. Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection. As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.

(i) Pharmacology and drug disposition. A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) Toxicology. (a) An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

(b) For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review.

(iii) For each nonclinical laboratory study subject to the good laboratory practice regulations under part 58, a statement that the study was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(9) Previous human experience with the investigational drug. A summary of previous human experience known to the applicant, if any, with the investigational drug. The information is required to include the following:

(i) If the investigational drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation's rationale. If the drug has been the subject of controlled trials, detailed information on such trials that is relevant to an assessment of the drug's effectiveness for the proposed investigational use(s) should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

(ii) If the drug is a combination of drugs previously investigated or marketed, the information required under paragraph (a)(9)(i) of this section should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

(iii) If the drug has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.

(10) Additional information. In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(i) Drug dependence and abuse potential. If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

(ii) Radioactive drugs. If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

(iii) Pediatric studies. Plans for assessing pediatric safety and effectiveness.

(iv) Other information. A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

(11) Relevant information. If requested by FDA, any other relevant information needed for review of the application.

(b) Information previously submitted. The sponsor ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously must identify the file by name, reference number, volume, and page number where the information can be found. A reference to information submitted to the agency by a person other than the sponsor is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

(c) Material in a foreign language. The sponsor shall submit an accurate and complete English translation of each part of the IND that is not in English. The sponsor shall also submit a copy of each original literature publication for which an English translation is submitted.

(d) Number of copies. The sponsor shall submit an original and two copies of all submissions to the IND file, including the original submission and all amendments and reports.

(e) Numbering of IND submissions. Each submission relating to an IND is required to be numbered serially using a single, three-digit serial number. The initial IND is required to be numbered 000; each subsequent submission (e.g., amendment, report, or correspondence) is required to be numbered chronologically in sequence.

(f) Identification of exception from informed consent. If the investigation involves an exception from informed consent under Sec. 50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in Sec. 50.24 of this chapter.

This form is available at URL <http://forms.psc.gov/forms/FDA/FDA-356h.pdf>

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION INVESTIGATIONAL NEW DRUG APPLICATION (IND) <i>(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)</i>		Form Approved: OMB No. 0910-0014. Expiration Date: September 30, 2002 See OMB Statement on Reverse.
1. NAME OF SPONSOR		2. DATE OF SUBMISSION
3. ADDRESS (Number, Street, City, State and Zip Code)		4. TELEPHONE NUMBER (Include Area Code)
5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code)		6. IND NUMBER (If previously assigned)
7. INDICATION(S) (Covered by this submission)		
8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: <input type="checkbox"/> PHASE 1 <input type="checkbox"/> PHASE 2 <input type="checkbox"/> PHASE 3 <input type="checkbox"/> OTHER _____ (Specify)		
9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR Part 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION		
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.		SERIAL NUMBER _____
11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply) <input type="checkbox"/> INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) <input type="checkbox"/> RESPONSE TO CLINICAL HOLD		
PROTOCOL AMENDMENT(S): <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> CHANGE IN PROTOCOL <input type="checkbox"/> NEW INVESTIGATOR	INFORMATION AMENDMENT(S): <input type="checkbox"/> CHEMISTRY/MICROBIOLOGY <input type="checkbox"/> PHARMACOLOGY/TOXICOLOGY <input type="checkbox"/> CLINICAL	IND SAFETY REPORT(S): <input type="checkbox"/> INITIAL WRITTEN REPORT <input type="checkbox"/> FOLLOW-UP TO A WRITTEN REPORT
<input type="checkbox"/> RESPONSE TO FDA REQUEST FOR INFORMATION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> GENERAL CORRESPONDENCE		
<input type="checkbox"/> REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED <input type="checkbox"/> OTHER _____ (Specify)		
CHECK ONLY IF APPLICABLE		
JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.		
<input type="checkbox"/> TREATMENT IND 21 CFR 312.35(b) <input type="checkbox"/> TREATMENT PROTOCOL 21 CFR 312.35(a) <input type="checkbox"/> CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)		
FOR FDA USE ONLY		
CDOR/IND/DGD RECEIPT STAMP	DOR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

12. CONTENTS OF APPLICATION		
This application contains the following items: <i>(Check all that apply)</i>		
<input type="checkbox"/> 1. Form FDA 1571 [21 CFR 312.23(a)(1)] <input type="checkbox"/> 2. Table of Contents [21 CFR 312.23(a)(2)] <input type="checkbox"/> 3. Introductory statement [21 CFR 312.23(a)(3)] <input type="checkbox"/> 4. General Investigational plan [21 CFR 312.23(a)(3)] <input type="checkbox"/> 5. Investigator's brochure [21 CFR 312.23(a)(5)] <input type="checkbox"/> 6. Protocol(s) [21 CFR 312.23(a)(6)] <ul style="list-style-type: none"> <input type="checkbox"/> a. Study protocol(s) [21 CFR 312.23(a)(6)] <input type="checkbox"/> b. Investigator data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572 <input type="checkbox"/> c. Facilities data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572 <input type="checkbox"/> d. Institutional Review Board data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572 <input type="checkbox"/> 7. Chemistry, manufacturing, and control data [21 CFR 312.23(a)(7)] <ul style="list-style-type: none"> <input type="checkbox"/> Environmental assessment or claim for exclusion [21 CFR 312.23(a)(7)(iv)(e)] <input type="checkbox"/> 8. Pharmacology and toxicology data [21 CFR 312.23(a)(8)] <input type="checkbox"/> 9. Previous human experience [21 CFR 312.23(a)(9)] <input type="checkbox"/> 10. Additional information [21 CFR 312.23(a)(10)]		
13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? <input type="checkbox"/> YES <input type="checkbox"/> NO IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? <input type="checkbox"/> YES <input type="checkbox"/> NO IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.		
14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS		
15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG		
I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.		
16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
18. ADDRESS (Number, Street, City, State and Zip Code)	19. TELEPHONE NUMBER (Include Area Code)	20. DATE
(WARNING: A willful false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.) Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852		
Food and Drug Administration CDER (HFD-99) 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852	*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*
Please DO NOT RETURN this application to this address.		

Appendix 5B - Investigational Device Exemption

Revised as of April 1, 2001
CFR TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION,
DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 812--INVESTIGATIONAL DEVICE EXEMPTIONS

Subpart A--General Provisions

Sec. 812.2 Applicability.

(a) General. This part applies to all clinical investigations of devices to determine safety and effectiveness, except as provided in paragraph (c) of this section.

(b) Abbreviated requirements. The following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under Sec. 812.20(a) that approval of an application is required:

(1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:

(i) Labels the device in accordance with Sec. 812.5;

(ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;

(iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under Sec. 56.109(c).

(iv) Complies with the requirements of Sec. 812.46 with respect to monitoring investigations;

(v) Maintains the records required under Sec. 812.140(b) (4) and (5) and makes the reports required under Sec. 812.150(b) (1) through (3) and (5) through (10);

(vi) Ensures that participating investigators maintain the records required by Sec. 812.140(a)(3)(i) and make the reports required under Sec. 812.150(a) (1), (2), (5), and (7); and

(vii) Complies with the prohibitions in Sec. 812.7 against promotion and other practices.

(2) An investigation of a device other than one subject to paragraph (e) of this section, if the investigation was begun on or before July 16, 1980, and to be completed, and is completed, on or before January 19, 1981.

(c) Exempted investigations. This part, with the exception of Sec. 812.119, does not apply to investigations of the following categories of devices:

(1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

(2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

(3) A diagnostic device, if the sponsor complies with applicable requirements in Sec. 809.10(c) and if the testing:

- (i) Is noninvasive,
- (ii) Does not require an invasive sampling procedure that presents significant risk,
- (iii) Does not by design or intention introduce energy into a subject, and
- (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

(4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

(5) A device intended solely for veterinary use.

(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with Sec. 812.5(c).

(7) A custom device as defined in Sec. 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

(d) Limit on certain exemptions. In the case of class II or class III device described in paragraph (c)(1) or (2) of this section, this part applies beginning on the date stipulated in an FDA regulation or order that calls for the submission of premarket approval applications for an unapproved class III device, or establishes a performance standard for a class II device.

(e) Investigations subject to IND's. A sponsor that, on July 16, 1980, has an effective investigational new drug application (IND) for an investigation of a device shall continue to comply with the requirements of part 312 until 90 days after that date. To continue the investigation after that date, a sponsor shall comply with paragraph (b)(1) of this section, if the device is not a significant risk device, or shall have obtained FDA approval under Sec. 812.30 of an IDE application for the investigation of the device.

Appendix 6 – Internal Operating Procedures [from Bionetics IOP-001]

Appendix 6A

MEDICAL CLEARANCE SUMMARY

NOTE: Screening H&P:

Medical History & Physical Examination
Physician Present, Valid for 1 Year.

Screening Max TMX:

Physician Present, Valid for 3 Years.

1. Screening H&P and Screening Max TMX:

LBNP(Max and Submax)

Max TMX

Max Cycle Ergometry

Protocols in which the Maximal Aerobic Capacity will be approached (70% of Max Predicted Heart Rate)

2. Screening H&P

Muscle Biopsy

Airpack and Protective suit Testing not involving Aerobic Stress

Barocuff

EMS Venous Compliance

Weight Training Protocols

(such as Kin Com, Con Ecc)

3. Abbreviated H&P

A review of the medical history, with further questioning, physical examination, and/or investigations as indicated.

This is the minimum medical requirement for any testing requiring medical coverage. This will include all remaining tests not listed above which require medical coverage (e.g. outside investigators having medical clearances from their sponsoring organization, and SLSTP participants receiving physicals prior to arrival).

NOTE: Screening H&P:

Medical History and Physical Examination

Physician Present, Valid for 1 Year.

Screening Max TMX:

Physician Present, Valid for 3 Years.

Medical Monitoring Requirements:

1. Physician and Nurses present in room:

Screening Max TMX
Max LBNP

2. Physician On-call in the building
Nurse present in room:

Max TMX and Submax TMX
Initial Barocuff
Initial EMS
LBNP to -50 mm Hg (Submax)
Max and Submax Cycle Ergometry
Muscle Biopsy
Airpack and Rescue Equipment Testing:
 Judged on a Case-by-Case Basis.

3. Physician on-call in the building:
To be determined by IRB.

4. Physician and/or Nurse on-call Off-Center:
To be determined by IRB.

5. No coverage required:

Post Initial Barocuff(Pending Review of the Protocol)
Post Initial EMS (Pending Review of the Protocol)
Phlebotomy
Cybex and Kin-com
Pulmonary Function Tests
Water Immersion Weighing
Weight Training
Other Vestibular or Perceptual Testing not involving a Sled or Rotating Chair Venous
 Compliance Anthropometry
Surface EMG

Appendix 6B

MEDICAL COVERAGE OF RESEARCH PROTOCOLS

- A. KSC/In-House Stress Laboratory Testing (e.g. approved experiment protocols, equipment evaluation) using Human Subjects and Requiring Medical Coverage.
 - 1. A physician shall oversee and interpret the initial subject screening examination for each research protocol. The examining physician grants approval for global or designated participation and will detail any restriction, limitations, or waiver considerations, utilizing consultation where appropriate.
 - 2. A physician shall be present during the screening treadmill stress test, and Max LBNP test.
 - 3. A physician shall be present during a maximal treadmill stress test and Max cycle ergometry if one has not been performed during the last 3 years.
 - 4. Air pack and rescue gear certification medical coverage will be determined on a case-by-case or study by study basis.
 - 5. For any test not requiring a physician in attendance, a nurse with Advanced Cardiac Life Support (ACLS) training shall be present in the room, and a physician must be present at a predetermined location in the O&C Building (unless specifically excepted, as in section D. below). This will include initial barocuff tolerance testing or exposure, submax LBNP and submax cycle ergometry.
 - 6. A physician may choose to be present during any test he or she thinks requires direct surveillance based on medical evaluation of the subject or the content of the protocol.
 - 7. The medical monitor, physician or nurse shall have absolute authority to limit or terminate a test. This authority shall be exercised judiciously but firmly.
 - 8. The engineer test conductor and the physiologist/Principal Investigator (PI) may also call for a "Test Stop". This should, however, be done in consultation with the medical monitor and other testing officials to assure minimum discomfort or danger to the subject.
- B. KSC/In-House muscle laboratory Testing or Procedures, muscle biopsy and electromyostimulation (EMS) using Human Subjects and Requiring Medical Coverage.
 - 1. A physician must be present at a predetermined location in the O&C Building, except as described in section D.
 - 2. A physician may choose to be present during any medical test he or she thinks requires direct surveillance based on medical evaluation of the subject or the content of the protocol. In established subjects with no history of complications from prior or current protocols, barocuff and EMS, coverage may not be required.
 - 3. The medical monitor, physician or nurse, shall have absolute authority to limit or terminate a test. This authority shall be exercised judiciously but firmly.

4. The engineer test conductor and the physiologists/PI may also call for a "Test Stop". This should, however, be done in consultation with the medical monitor and other testing officials to assure minimum discomfort or danger to the subject.
- C. Life Sciences Flight Experiments Testing in the BDCF.
1. A physician must be present at a predetermined location in the O&C Building, except as described in section D. During Post Flight Life Science experiments there will be a Physician present at all times.
 2. A physician may choose to be present during any medical test he or she thinks requires direct surveillance based on medical evaluation of the subject or the content of the protocol. In established subjects with no history of complications from prior or current protocols, barocuff and EMS coverage may not be required.
 3. The medical monitor, physician or nurse, shall have absolute authority to limit or terminate a test. This authority shall be exercised judiciously but firmly.
 4. The engineer test conductor and the physiologists/PI may also call for a "Test Stop". This should, however, be done in consultation with the medical monitor and other testing officials to assure minimum discomfort or danger to the subject.
- D. The following procedures do not require medical coverage and may not require the screening physical examination and treadmill stress test. Such medical clearance will be made by a physician's medical history review, interview and/or physical examination if indicated. Approvals will be made on a case-by-case basis.
1. Phlebotomy.
 2. Routine, noninvasive, nonstressful data gathering.

EXAMPLES

Skin folds
Anthropometric Measurements
Cybex on screened subjects
Pulmonary Function Tests
Cardiovascular Monitoring
Water Immersion Weighing Procedures

3. Non-treadmill Physical Fitness Testing or Training.

EXAMPLES

KinCom
Push-ups
Sit-ups
Pull-ups
Squat Thrusts
Weight Lifting

4. Vestibular or perceptual testing not involving the sled or rotating chair.

5. Post-initial barocuff and EMS in subjects with no history of significant complications from any previous or current protocol may not require medical coverage.
6. Non-stress equipment testing by employees medically certified to use such equipment.
- E. Outside Investigators: Medical coverage shall be worked out on a case-by-case basis by mutual agreement between JSC Medical Operations Branch and KSC Biomedical Office when involving Flight Crew.

Should outside investigators desire to provide their own subjects and medical monitor, all guidelines in A and/or B above must be met with the KSC physician-in-charge, designated by KSC Biomedical Office, having approved such medical coverage.

TERMINOLOGY

A. TREADMILL PROTOCOLS

1. "TURN OFF THE TREADMILL"
Immediately STOP treadmill, regardless of grade and speed, and remove subject from treadmill.
2. "BEGIN COOLDOWN"
Immediately lower treadmill speed and grade to cool-down level.
3. "THIS IS THE LAST MINUTE OF EXERCISE"
Complete current minute at current grade and speed then lower treadmill speed and grade to cool-down level.

B. LBNP PROTOCOLS

"STOP THE TEST"

Immediately return the pressure to baseline level.

C. REMAINDER OF PROTOCOLS

"STOP THE TEST"

Immediately discontinue the procedure.

EMERGENCY PROTOCOL

A. Laboratory Personnel

The medical and/or subject monitor should be aware of:

1. Subjects general physical condition(e.g., general fitness level, risk factors, medical problems, medications, allergies).
2. Subject's resting heart rate and blood pressure.

B. Personnel Preparedness

All personnel in the laboratory should be constantly alert for the following:

1. Decrease in blood pressure significantly below subjects resting blood pressure.
2. Significant decrease in heart rate, especially associated with workload increase (sign of cardiac decompensation).
3. Systolic blood pressure equal to or greater than 250mmhg.
4. Diastolic blood pressure greater than 110 mm Hg.
5. Significant increase in heart rate, equal to or greater than maximum predicted heart rate, early in protocol at relatively low workloads.
6. Arrhythmias.
7. Cyanosis, cold clammy skin, muscle twitching, dilated pupils.
8. Chest pain, left arm pain.
9. Increasing shortness of breath.
10. Nausea, pallor, lightheadedness.

C. Emergency Management

If any of the above conditions occur:

1. If Physician is present, he or she will evaluate.
2. If Physician is not present and there are no symptoms or distress (non-emergency event):
 - a. TREADMILL: Stop the test and begin cool-down.
 - b. LBNP: Stop the test and return pressure to baseline level.
3. If physician is not present and there are symptoms or distress (emergency event):
 - a. TREADMILL: Turn off the Treadmill and remove subject from treadmill.
 - b. LBNP: Stop the test.
 - c. Page the physician.
 - d. TREADMILL: Remove mouthpiece and nose clip.
Lay subject supine on the floor and observe closely.
LBNP: Loosen the rubber waist seal and remove LBNP wooden waist seal and observe closely.
 - e. Establish responsiveness. Shake subject and call out, 'Are you O.K.?' If subject is unresponsive, call for help.
 - f. Follow Advanced Cardiac Life Support (ACLS) algorithms on Crash Cart. These are to be kept current in exact duplication of the recommended ACLS algorithms from American Heart Association.

Appendix 6C

BIOMEDICAL LABORATORY TEAM EMERGENCY RESPONSE

A. Participants

The following personnel are typically in the laboratory area:

1. Registered Nurse (RN) - in test area.
2. Engineer - in test area.
3. Engineering Technician - in test area
4. Medical Technologist - in lab area.
5. Physician - in test area or on-call (pager).
6. Principal Investigator - for certain tests only.

B. Duties

1. Registered Nurse (RN):
 - -Assess patient and direct CPR until physician arrives
 - -States "Medical Emergency call 911"
 - -Follow ACLS protocols
 - -Assist/perform IV access and drug administration
2. Engineer:
 - -Obtain crash cart
 - -Apply electrodes/hook-up EKG
 - -Obtain oxygen and suction
3. Engineering Technician:
 - -Call 911
 - -Page doctor on-call if not present
 - -Monitor BP and ECG if on-line
 - -Assist engineer
 - -Maintain voice log on magnetic tape.
4. Medical Technologist:
 - -Secure elevator/escort Emergency Medical Services (EMS)
 - -Manual BP if investigator not present
 - -Draw blood if needed.
5. Physician (MD):
 - -Assess patient
 - -States "Medical Emergency, call 911"
 - -On Scene Commander, directs ACLS protocols.

6. Principal Investigator:
 - -Take manual BP as directed
 - -Record emergency treatments and time (CPR, Defibrillation, Drugs, etc.)

C. Protocol

Administer CPR and ACLS as recommended by current American Heart Association guidelines.

1. Maintain laminated copies of urgent CPR and ACLS algorithms on all crash carts.
2. Registered nurse, Physician and Engineer are required to keep CPR certification current.
3. Registered nurse and Physician are required to maintain ACLS certification.
4. Engineer technicians, Medical technologist and Research investigators are urged to obtain CPR certification.

Appendix 6D

SUBJECT SCREENING PART I: SCREENING PHYSICAL EXAM

The purpose of the screening process is to medically qualify or disqualify potential research subjects to participate in a specific activity and/or study. The complete screening process consists of two parts:

- I. Screening physical examination.
- II. Screening treadmill stress test (maximal effort).

Screening requirements vary according to the specific research activity and/or study. These requirements are determined according to Biomedical Office Policy. Medical screening requirements must be defined prior to subject participation in research activities. For example, a completed medical history form reviewed by a physician may be the only requirement in some cases. In other instances a screening physical examination may be required. In yet other instances, a maximal effort treadmill stress test may be required in addition to the physical examination.

I. SCREENING PHYSICAL EXAMINATION

A. General Information and Preparation

1. If a screening physical examination is required, it is valid for one year.
2. Prior to scheduling a screening physical examination determine the availability of the subject, as well as the R.N., physician, and medical technologist who will provide support.
3. Scheduling is performed by the R. N., after receiving a request from the Principal Investigator of an upcoming study.
4. Screening physical examinations should be scheduled during the morning hours. For multiple exams, the first one is scheduled at 8:00 A.M. and successive exams are scheduled 30-45 minutes apart. The last exam should be scheduled no later than 10:30 A.M.
5. A screening packet is mailed to the subject in advance of the examination date. The screening packet contains the following:

Appointment Card
Instruction Sheet
Subject Information Sheet
Report of Medical History
Screening Questionnaire
Privacy Act Statement
Social Security Number Statement

The appointment Card will be filled out with the time of the subjects lab visit and physical.

The Instruction Sheet will inform the subject where to report and who to call if they have any questions or concerns.

The subject must bring in the completed forms on the exam date. If it is not possible to mail the screening packet to the subject prior to the examination date, the subject will complete the forms on the examination date.

Instruct the subject to fast for 12 hours prior to the exam. Sips of water are permissible. Explain to the subject what the exam will consist of and when and where to report.

B. Procedure

1. If the subject does not have a subject number, he/she will sign in the log book and will be assigned a subject number. If he/she already has a subject number, obtain the file prior to their examination.
2. The subject will have a blood sample drawn for chemistry and hematology. (Refer to Clinical Laboratory procedure manual for specific laboratory tests.)
3. The subject will give a urine sample for routine urinalysis after a blood sample is drawn.
4. Prior to the beginning of the examination the subject may have coffee, juice, and/or a snack.
5. The R.N. will perform the following:
 - height and weight
 - sitting blood pressure (right arm)
 - allergies
 - current medications
 - smoking history
 - type & frequency of current physical exercise
 - supine 12-lead electrocardiogram (ECG).
 - supine blood pressure (left arm).
6. The physician will then conduct a physical examination.
7. The R. N. will conduct a pulmonary function test (PFT). (Refer to PFT Procedure. IOP-.001.01.08)
8. The screening physical examination is then completed. If a treadmill stress test is required, refer to Part II of Subject Screening, IOP-001.01.06.

Appendix 6E

SUBJECT SCREENING

PART II: TREADMILL STRESS TEST

The standard treadmill stress test used in the Biomedical Stress Laboratory is a maximal effort graded exercise stress test. A maximal exercise test brings an individual to a level of workload intensity where fatigue or symptoms prohibit further exercise, or when maximal oxygen consumption (V02 max) is achieved and no further increase in heart rate occurs. Purposes of the TMX include:

1. Screening: to medically qualify or disqualify subjects who participate in research activities (valid for 3 years).
2. Research: to determine maximal aerobic capacity (V02 max) .
3. Clinical: to clinically evaluate an individual as requested by Biomedical Office physicians.

A. Definitions

1. Medical Monitor-is a physician or nurse who monitors the subjects medical condition throughout a test protocol utilizing EKG, vital sign parameters, and other objective data.
2. Subject Monitor-is a physician or nurse who watches the subject for toleration of testing procedures and physiological decompensation.

B. General Information and Preparation

1. Prerequisites to the TMX include: A complete screening physical examination and medical clearance by a physician within one year of the TMX (see Subject Screening Procedure, Part I. IOP-001.01.05).
2. Unless otherwise specified and approved by the Principal Investigator and physician, a modified Bruce protocol will be followed.
3. Verbal and written explanations/instructions will be given to the subject prior to the TMX test (see attachment, on page 8 of this IOP).
4. When scheduling the subject for the TMX test, instruct them on the length of time involved. Allow 1 1/2 - 2 hours for the TMX test from the time the subject arrives to the time the subject leaves the stress lab. (This includes time for a shower.)
5. The subject should not eat at least 2 hours prior to the TMX (to avoid exercise related nausea). Consumption of caffeinated beverages should be avoided prior to the TMX (to avoid caffeine related ECG abnormalities).
6. The subject will wear loose fitting exercise attire and comfortable running shoes.

C. Subject Preparation

1. Review subject's medical file. Determine if current contraindications to stress testing exist (i.e., medications, acute infection, recent injury).
2. Subject changes into exercise attire (leave shoes off).
3. Obtain height and weight measurement.
4. Subject puts on rubber soled shoes.
5. Sensor subject with electrodes for 12-Lead ECG (see 12 Lead ECG Sensoring Procedure-IOP-001-.01.07).
6. Review treadmill protocol and instructions with subject:
 - a. treadmill protocol (baseline, stages, recovery)
 - b. thumb signals (thumbs up to continue, down to stop)
 - c. mouthpiece, nose clip, blood pressure
 - d. test termination criteria

D. Protocol Preparation

1. Record subject and test data on lab board.
2. Check ECG for clarity.
3. Apply blood pressure cuff on right arm and secure with tape. The microphone is placed over the brachial artery on the inside of the upper arm between biceps and triceps.
4. Check BP for acceptable reading.
5. Secure nose clip in place.
6. Have subject insert Mouthpiece.
7. Have the subject stand at rest. This will allow for room air to purge, synchronization of the automated BP system, and starting of the recorders.

E. Bruce (modified) Treadmill Protocol

<u>Minute</u>	<u>Event</u>	<u>MPH</u>	<u>Grade</u>
1-4	Standing Rest	-	-
4-5	Warm-up walk	1.7	0%
5-8	Stage I	1.7	10%
8-11	Stage II 2.5	12%	
11-14	Stage III 3.4	14%	
14-17	Stage IV 4.2	16%	
17-20	Stage V 5.0	18%	
20-23	Stage VI 5.5	20%	
23-26	Stage VII 6.0	22%	

Immediately after the subject and/or medical monitor indicates to stop the test instruct the subject to grasp the handrail.

RECOVERY

<u>Minute</u>	<u>Event</u>	<u>MPH</u>	<u>Grade</u>
0-1	Walking cool-down	2.5	10%
1-5	Walking cool-down	1.7	0%
5-10	Standing recovery	-	-

A 10 minute recovery period (5 minutes of walking cool-down and 5 minutes of standing) will immediately follow termination of maximal exercise, unless clinically contraindicated.

During Standing Recovery-Shift weight every few seconds. Do not let the subject stand motionless for greater than 10 seconds.

F. Test Termination Criteria

1. Subject requests to stop.
2. V02 max is achieved.
3. Failure of the monitoring system.
4. Angina.
5. Two millimeters horizontal or down sloping ST-depression or elevation.
6. Sustained supraventricular tachycardia.
7. Ventricular tachycardia (3 or more successive PVCs).
8. Exercise induced left or right bundle branch block.
9. Any sudden significant drop (10 mm Hg) of systolic blood pressure, or failure of the systolic blood pressure to rise with an increase in exercise load after the initial adjustment period.
10. Lightheadedness, confusion, ataxia, pallor, cyanosis, nausea, or signs of severe peripheral circulatory insufficiency.
11. Excessive blood pressure rise: Verified Systolic greater than 250 mm Hg; Verified diastolic greater than 120mmHg.
12. R on T premature ventricular complexes.
13. Failure of the heart rate to increase with an increase in workload.
14. Onset of second or third degree heart block.
15. Multifocal PVCs.
16. Increasing ventricular ectopy (>30% of the total beats per minute).

G. Criteria for an Abnormal Exercise Test

1. One millimeter or more of exercise induced ST-segment depression or elevation relative to the Q-Q line, lasting .08 seconds or more from the J-point.
2. Chest discomfort typical of angina pectoris induced or increased by exercise.
3. Ventricular tachycardia or frequent (>30%) premature ventricular contractions, or multifocal premature ventricular contractions.
4. Exercise induced left or right bundle branch block.
5. Significant drop (greater than 10 mm Hg) in systolic blood pressure during exercise, or failure of the systolic blood pressure to rise with an increase in exercise intensity after the initial adjustment period.
6. Sustained supraventricular tachycardia.
7. R on T PVCs.
8. Exercise induced second or third degree heart block.
9. Post-exercise U-wave inversion.
10. Inappropriate bradycardia.

H. Post-Recovery

1. Remove nose clip and mouthpiece after the gas analyzer prints out final readout. Check with Technician before doing so.
2. Before disconnecting the monitoring leads near pre-exercise levels of heart rate and blood pressure should be obtained. The subject may sit down at this time.
3. Remove BP cuff after the Biomedical technician has secured it.
4. Remove sensors (see 12 Lead-IOP-001.01.07)
5. Discuss symptoms with subject-difficulties, pain, SOB.
6. Encourage Subject to shower, avoiding hot water.
Note: A CPR certified individual must remain in the lab, outside the shower until the subject is finished.
7. After reviewing the test data and symptoms, discuss test results with subject.
8. After the subject has departed, remove the mouthpiece from the counter-weight and disinfect (see Mouthpiece Disinfection procedure-IOP-001.01-09).
9. Collect, arrange and file TMX data and document test results in subject record.

SUMMARY OF ROLES DURING

TREADMILL STRESS TEST

ENGINEER:

- -Operates treadmill and gas analyzer equipment.
- -Annotates tape and starts test clock.
- -Records blood pressures and elapsed time on ECG recording.

TECHNICIAN:

- -Calibrates gas analyzer, and ECG cart to magnetic tape and strip chart recorders.
- -Operates horizontal strip chart recorder.
- -Obtains and records blood pressure every two minutes.
- -Operates MADAM computer, and 14 cm magnetic tape recorders.

PHYSICIAN:

- -Medical monitor during all clinical treadmill stress tests.
- -Medical monitor during screening treadmill stress tests if the subject hasn't had a screening treadmill within the past 3 years.

REGISTERED NURSE:

- -Subject monitor when physician is present.
- -Medical monitor when physician is absent.
- -Physiological data recorder when required.
- -Discuss test results with subject after completion of test.

Attachment

TREADMILL STRESS TEST INFORMATION

You have been scheduled to come to the Biomedical Stress Lab, O&C Building, room 3219, on _____ at _____, for a stress test. Please eat a light meal, avoiding caffeine, at least two hours before the test.

Please remember to bring comfortable running shoes, shorts and a loose fitting shirt with you. When you arrive at the lab, you will change into these clothes, your height and weight will be measured, and ten electrode sensors will be placed on your chest to monitor heart rate and rhythm during the stress test. You will then be ready to walk/run on the treadmill.

Throughout the test, you will be breathing through a mouthpiece in order to measure your maximum oxygen capacity. Blood pressure will also be monitored during the stress test. Your test will be monitored by an engineer, a physician and a registered nurse. The treadmill walk will get progressively steeper and faster until you reach your physiological limit or "max". Your legs or lungs will tell you when this point is reached. A slow walk, "cool down period", will follow. Finally, the test concludes with a five minute standing recovery period. You may then shower in our facility. The results of your treadmill will be discussed with you after the test.

The entire procedure will require approximately one and one-half hours of your time.

If you have any questions about the test, please feel free to contact us at (_____). Your interest and cooperation in our program is appreciated, and we look forward to including you in our subject pool.

Thank you.