EPA ORDER

Classification No.: 1000.17 Change A1

Approval Date: July 30, 1999

POLICY AND PROCEDURES ON PROTECTION OF HUMAN RESEARCH SUBJECTS IN EPA CONDUCTED OR SUPPORTED RESEARCH

1. PURPOSE. This Order supersedes EPA Order 1000.17 *Policy and Procedures on Protection of Human Subjects*, October 25, 1977, including changes thereto, and establishes EPA-wide responsibilities and policies for the use of human subjects in research.

2. APPLICABILITY. This Order applies to all research covered by 40 CFR Part 26 (*The Common Rule)* (attached hereto as Appendix A), i.e., all research involving human subjects conducted or supported by EPA. It also covers the determination of which research involving human subjects is exempt from the Common Rule. Furthermore all other EPA policies and other official EPA actions involving EPA conducted or supported research with human subjects shall cross reference or include this Order.

3. DEFINITIONS.

a. *Research.* Research means a systematic investigation, including research, development, testing and evaluation designed to develop or contribute to generalizable knowledge. Note that some demonstration and service programs may include research activities. 40 CFR 26.102(d).

b. *Exempt research*. Research studies that may be found to be exempt are identified in 40 CFR 26.101(b). An example of such exempted research is that involving the analysis of existing data sets, documents or specimens if they are publicly available or recorded in a manner such that the subjects cannot be identified.

c. *Human exposure research.* 40 CFR Part 26 does not encompass research designed to estimate potential human exposure if that research falls outside that defined in section 26.101. However it does encompass human exposure research that meets any of the following: (1) Research that includes the gathering of physiological measurements (e.g., monitoring a subject's cardiorespiratory performance) or the collection of body fluids, tissue or expired air from subjects; or (2) Research that requires subjects to perform specific tasks other than their normal activities or

manipulates their environment (e.g., modifies their exposure); or (3) Research that gathers or records private information (as defined in 40 CFR 26.102 (f)(2)) in a manner that associates such information with an identifiable subject.

d. *Human subject* [or variants such as *human research 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. 40 CFR 26.102 (f).

e. *Material non-compliance* means failure to comply with those requirements of *The Common Rule* and this Order necessary to carry out their essential policies of protecting human subjects of research from anything more than minimal risk. This definition is adapted from common law concepts of material compliance and substantial compliance.

f. *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. 40 CFR 26.102(i).

g. *Risk of substantial injury* means a significant probability that the research may lead to a substantial impairment of normal activities or long-lasting or irreversible damage to the health of a human subject. This definition is adapted from the definition of *significant adverse reactions* in the Toxic Substances Control Act section 8 reporting rule at 40 CFR 717.3(i).

4. POLICY. In dealing with human research subjects it is EPA policy that:

a. All research shall comply with *The Common Rule, i.e.* 40 CFR Part 26 (Appendix A) and with this Order.

b. All human subject research studies supported by EPA must either be approved or be determined to be exempt research by the EPA Human Subjects Research Review Official (the Review Official) before any contract, grant, cooperative agreement, cooperative research and development agreement [CRADA], interagency agreement, or any formal agreement involving EPA support of such studies is awarded or entered into. All human research studies conducted by EPA also must be approved or determined to be exempt by the Review Official before work can start. Approval will be given only to research which complies with subsection 4.a. above.

c. There is a presumption that studies involving risk of substantial injury to a human subject from the conduct of the study and that studies testing for irreversible health effects in humans will not be approved, even if the studies otherwise meet the requirements of subsection 4.a, unless strongly persuasive additional justification acceptable to the Review Official is submitted.

5. REQUIREMENTS. To obtain approval by the Review Official, submitted documents must include:

a. Documentation showing to the satisfaction of the Review Official that each institution conducting research covered by 40 CFR Part 26 has an approved program. This is generally accomplished by documenting that the institution holds a multiple project assurance [MPA] which is approved by and is on file with the U.S. Department of Health and Human Services' [HHS's] Office for Protection from Research Risks [OPRR], which is currently approved for federal-wide use by the Secretary of HHS, and which is not conditioned in any way as to be inapplicable to the proposed human subjects research. (The MPA is a document submitted to HHS by the institution assuring compliance with the Common Rule and giving some particulars as to how compliance will be assured, 40 CFR 26.103.) The proper completion and submission of Optional Form 310, *Protection of Human Subjects, Assurance Identification/Certification/Declaration* (Appendix B) fulfills this requirement. Certain special circumstances (e.g., the institution does not have an applicable HHS assurance) may require the negotiation of an EPA assurance as described in 40 CFR 26.103.

b. A written approval from each institution's Institutional Review Board [IRB] that the proposed research has been reviewed and approved in accordance with the assurance. The proper completion and submission of Optional Form 310 also fulfills this requirement. This review may be an expedited one if allowed by 40 CFR 26.110 and the research activities are on the current HHS list of activities eligible for expedited review. (Appendix C is the current HHS list; the list may be revised.)

c. A copy of the research proposal, including the protocol.

d. A copy of the consent form to be used and, when appropriate, a description of the procedures to be used in obtaining effective informed consent.

6. RESPONSIBILITIES. The following EPA organizational and individual responsibilities apply to the development and management of any research study involving human subjects.

a. Review Official

(1) The Review Official, currently the Director of the National Center for Environmental Research and Quality Assurance [NCERQA], is responsible for reviewing all EPA conducted or supported research studies involving human subjects. The Review Official determines whether the proposed study is subject to this Order or exempt. If not exempt, the Review Official determines compliance with this Order and, if warranted, approves all research studies involving human subjects covered by 40 CFR Part 26. Among other things, the Review Official will determine that the cited HHS MPA or equivalent procedure is applicable to the proposed study and that it is currently in force. All determinations that proposed research is exempt, and approvals will be in writing.

(2) The Review Official may grant approval of a study protocol which is used repetitively. All changes or modifications must be reviewed and approved by the applicable IRB.

(3) The Review Official may withhold approval of any proposal if it does not adequately protect the rights and welfare of the human subjects. The Review Official will provide a written explanation to the requestor for such withholding. Such letter will contain an explanation of the applicable appeal rights. The submitting program or regional office may revise the proposal to address the concerns of the Review Official and resubmit the proposal. Ordinarily the Review Official's decision is expected in 30 days or fewer. The decision to withhold approval may be appealed as set out in subsection 6.d., below.

(4) The Review Official has the authority to have any study suspended or terminated (i) if it is found to be in material noncompliance with the assurance or with the IRB approved methods and procedures, or (ii) if HHS withdraws its approval of the institution's MPA, or (iii) if there is good reason to believe that the rights and welfare of the human research subjects are not being adequately protected, or (iv) if there has been unexpected serious harm to one or more human subjects. If a non-EPA institution is involved, the Award Official/Contracting Officer will be informed in writing of the reason for the suspension or termination and the Award Official/Contracting Officer will immediately notify the institution in writing. If the study has been suspended, the suspension shall remain in effect until the deficiencies have been corrected and the Review Official has approved resumption of work. Decisions to suspend or terminate a study may be appealed as set out in subsection 6.d., below. Studies affected by a suspension or termination shall remain in suspended or terminated status pending conclusion of the appeal.

(5) The Review Official may establish and maintain an appropriate group (e.g., an Ethics Advisory Board) to advise and assist him/her in carrying out these responsibilities.

(6) The Review Official may issue EPA MPAs or single project assurances [SPAs] to an entity not having an HHS MPA but otherwise meeting the requirements of 40 CFR Part 26 and this Order. EPA MPAs will be applicable to EPA supported research only.

b. EPA Program Office, Regional Office, Project Officer

(1) The EPA program or regional office that conducts or supports research covered by this Order is responsible for compliance with it. In the first instance the office will decide whether the project involves "human subjects" and is "research" as per 3(a) and 3(d) above, and hence is a covered project. Each covered project will have a project officer from or reporting to the responsible office.

(2) The program or regional office supporting extramural research involving human research subjects is responsible for notifying the EPA Award Official/Contracting Officer that human subjects are involved.

(3) The project officer is responsible, *inter alia*, for monitoring the conduct of the study for compliance with the agreed upon procedures and methods for the protection of the rights and welfare of human subjects. Such monitoring may involve various management techniques such as site visits, review of documentation, and communication with the researchers. Should the project officer discover material noncompliance with the assurance or with the IRB approved methods and procedures, the project officer shall notify his/her management, the Award Official/Contracting Officer (when applicable), and the Review Official at once.

c. EPA Award Official/Contracting Officer

(1) The EPA Award Official/Contracting Officer is responsible for ensuring that the written approval or exemption determination from the Review Official is submitted as part of the funding package prior to awarding or entering into any contract, grant, cooperative agreement, CRADA, interagency agreement, or any formal agreement involving research covered by this Order. He/she is responsible for including within the contract, grant, cooperative agreement, CRADA, or other formal agreement, except interagency agreements, a clause or special condition requiring compliance with EPA's regulations, policies and

procedures for the protection of human research subjects as described or referenced in this Order. For interagency agreements he/she is responsible for including a clause or special condition requiring protection of human research subjects as per their own version of the Common Rule. Should the department or agency not be a signatory to the Common Rule, the clause or special condition will require compliance with EPA's regulations, policies and procedures as described or referenced in this Order. If the project has human subjects but is not research he/she must assure that an explanation of why the project is not research is included in the funding package.

(2) The Award Official/Contracting Officer will immediately notify the institution in writing when a study is terminated or suspended, and include in such notification a statement of the basis for the termination or suspension.

d. The Administrator

(1) If an institution wishes to appeal the withholding of approval for a new study (paragraph 6.a.(3)), the suspension of a study because of deficiencies (paragraph 6.a.(4)), or the termination of a study because of deficiencies (paragraph 6.a.(4)), the institution may do so by delivering a written appeal within thirty (30) days of the date of receipt of notification of the action to the Administrator or his/her designee, U.S. Environmental Protection Agency, Washington, DC 20460. The appeal shall set forth in detail the decision being appealed and the basis of the appeal and may include supporting materials.

(2) The Administrator or his/her designee will respond in writing within thirty (30) days of receipt of the appeal, which time can be extended for good cause by the Administrator or his/her designee.

e. All EPA Employees Any EPA employee who has knowledge that EPA supported or conducted research has been associated with unexpected serious harm to one or more human subjects shall immediately notify the Review Official.

7. FOREIGN STUDIES. Procedures followed in foreign countries to protect human research subjects may differ from those set forth in 40 CFR Part 26 (*The Common Rule*). In these circumstances, the Review Official may approve the substitution of foreign procedures for the requirements of the Common Rule if he/she determines that such procedures offer protection that is "at least equivalent" to that provided by *The Common Rule* (40 CFR 26.101(h)). As a general guide, studies conducted by foreign institutions which comply with guidelines consistent with the World Medical Assembly Declaration (*Declaration of Helsinki*, amended 1996), issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized, may be approved. Guidelines to be considered in evaluating foreign studies and the protection of human research subjects can be found in Appendix D.

8. SAVING PROVISION. Any and all modifications to 40 CFR Part 26 will automatically become part of this Order on the effective date of such modifications.

9. SUPERSESSION. This Order supersedes EPA Order 1000.17 *Policy and Procedures on Protection of Human Subjects*, October 25, 1977.

Approval: /s/
Romulo L. Diaz, Jr.
Assistant Administrator for
Administration and Resources Management

APPENDIX A

[Code of Federal Regulations] [Title 40, Volume 1, Parts 1 to 49] [Revised as of July 1, 1997]
From the U.S. Government Printing Office via GPO Access [CITE: 40CFR26] [Page 261-272]

TITLE 40--PROTECTION OF ENVIRONMENT

CHAPTER I--ENVIRONMENTAL PROTECTION AGENCY

PART 26--PROTECTION OF HUMAN SUBJECTS

Sec.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b).
Source: 56 FR 28012, 28022, June 18, 1991, unless otherwise noted.

Sec. 26.101 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. 26.102(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. 26.102(e) must be reviewed and approved, in compliance with Sec. 26.101, Sec. 26.102, and Sec. 26.107 through Sec. 26.117 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.\1\

\1\ 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.

[56 FR 28012, 28022, June 18, 1991, 56 FR 29756, June 28, 1991]

Sec. 26.102 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. 26.103 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 federalwide 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. 26.101 (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 recordkeeping 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. 26.103(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. 26.101 (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. 26.103 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. 26.103 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.

(Approved by the Office of Management and Budget under control number 9999-0020)

[56 FR 28012, 28022, June 18, 1991, 56 FR 29756, June 28, 1991]

Secs. 26.104--26.106 [Reserved]

Sec. 26.107 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. 26.108 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. 26.103(b)(4) and, to the extent required by, Sec. 26.103(b)(5).

(b) Except when an expedited review procedure is used (see Sec. 26.110), 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. 26.109 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. 26.116. The IRB may require that information, in addition to that specifically mentioned in Sec. 26.116, 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. 26.117.

(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.

(Approved by the Office of Management and Budget under control number 9999-0020)

Sec. 26.110 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. 26.108(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. 26.111 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. 26.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by Sec. 26.117.

(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. 26.112 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. 26.113 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.

(Approved by the Office of Management and Budget under control number 9999-0020)

Sec. 26.114 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. 26.115 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. 26.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in Sec. 26.103(b)(4) and Sec. 26.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by Sec. 26.116(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.

(Approved by the Office of Management and Budget under control number 9999-0020)

Sec. 26.116 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.

(Approved by the Office of Management and Budget under control number 9999-0020)

Sec. 26.117 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. 26.116. 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. 26.116 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.

(Approved by the Office of Management and Budget under control number 9999-0020)

Sec. 26.118 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. 26.101 (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. 26.119 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. 26.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

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. 26.121 [Reserved]

Sec. 26.122 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. 26.123 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. 26.124 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.

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APPENDIX B

Protection of Human Subjects
Assurance Identification/Certification/Declaration
(Common Federal Rule)

Policy: Research activities involving human subjects may not be conducted or supported by the Departments and Agencies adopting the Common Rule (56FR28003, June 18, 1991) unless the activities are exempt from or approved in accordance with the common rule. See section 101(b) the common rule for exemptions. Institutions submitting applications or proposals for support must submit certification or appropriate Institutional Review Board (IRB) review and approval to the Department or Agency in accordance with the common rule.

Institutions with an assurance of compliance that covers the research to be conducted on file with the Department, Agency, or the Department of Health and Human Services (HHS) should submit certification of IRB review and approval with each application or proposal unless otherwise advised by the Department or Agency. Institutions which do not have such an assurance must submit an assurance and certification of IRB review and approval within 30 days of a written request from the Department or Agency.

1. Request Type	2. Type of Mechanism	3. Name of Federal Department or Agency and, if known, Application or Proposal Identification No.
☐ ORIGINAL ☐ FOLLOWUP ☐ EXEMPTION	☐ GRANT ☐ CONTRACT ☐ FELLOWSHIP ☐ COOPERATIVE AGREEMENT ☐ OTHER:_____	
4. Title of Application or Activity		5. Name of Principal Investigator, Program Director, Fellow, or Other

6. Assurance Status of this Project *(Respond to one of the following)*

☐ This Assurance, on file with Department of Health and Human Services, covers this activity:
Assurance identification no.—_____ IRB identification no. _____

☐ This Assurance, on file with *(agency/dept)*_____, covers this activity.
Assurance identification no._____ IRB identification no._____*(if applicable)*

☐ No assurance has been filed for this project. This institution declares that it will provide an Assurance and Certification of IRB review and approval upon request.

☐ Exemption Status: Human subjects are involved, but this activity qualifies for exemption under Section 101(b), paragraph_____.

7. Certification of IRB Review (Respond to one of the following IF you have an Assurance on file)

☐ This activity has been reviewed and approved by the IRB in accordance with the common rule and any other governing regulations or subparts on *(date)*_____ by: ☐ Full IRB Review or ☐ Expedited Review

☐ This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by the common rule will be reviewed and approved before they are initiated and that appropriate further certification will be submitted.

8. Comments

9. The official signing below certifies that the information provided above is correct and that, as required, future reviews will be performed and certification will be provided.		10. Name and Address of Institution
11. Phone No. *(with area code)*	12. Fax No. *(with area code)*	
13. Name of Official		14. Title
15. Signature		16. Date

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OPTIONAL FORM 310(Rev. 1/98)
Sponsored by HHS/NIH

Public reporting burden for this collection of information is estimated to average less than an hour per response. 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. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: NIH, Project Clearance Office, 6701 Rockledge Drive, MSC 7730, Bethesda, Md. 20892-7730, ATTN: PRA 0925-0418. *Do not return the completed form to this address.*

APPENDIX C

Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure[1]

Applicability

(A) Research activities that: (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

(B) The categories in this list apply regardless of the age of subjects, except as noted.

(C) The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

(D) The expedited review procedure may not be used for classified research involving human subjects.

(E) IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

(F) Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) from other adults and children[2], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency

with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

(b) where no subjects have been enrolled and no additional risks have been identified; or

(c) where the remaining research activities are limited to data analysis

(9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

[1] An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110.
[2] Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a). Source: 63 FR 60364-60367, November 9, 1998.

APPENDIX D

BACKGROUND INFORMATION FOR U.S. GOVERNMENT DEPARTMENT AND AGENCY PERSONNEL

PROTECTION OF HUMAN SUBJECTS IN STUDIES CONDUCTED OUTSIDE THE UNITED STATES

This information package is provided to guide U.S. Government personnel who design, review or carry out research involving human subjects in foreign settings. The purpose of these materials is to inform the reviewing U.S. Government officials of the responsibilities of Departments and Agencies. These Departments *and* Agencies *must* adhere to the requirements of U.S. law and Federal regulations governing the protection of human subjects involved in research conducted, supported or otherwise subject to regulation by the Federal Government outside the U.S. The Common Rule (Federal Policy for the Protection of Human Subjects - copy enclosed [Appendix A]) states that any research involving human subjects, supported or conducted in whole or in part by Federal Departments or Agencies, in either foreign or domestic settings, is subject to the Common Rule. In the event that research does not meet the standards of the Common Rule, the Department or Agency must either (1) assure that any deficiency is corrected or (2) obtain a waiver from the official designated by the Common Rule as authorized to grant waivers. Unless the Common Rule standards can be met, Federal Departments and Agencies will not be able to participate in the research.

Procedures normally followed in foreign countries to protect human subjects may differ from those in the Common Rule. If a Department or Agency Head or designee determines that the procedures prescribed by the foreign institution afford protections that are “at least equivalent" to those in the Common Rule, the Department or Agency Head may approve the substitution of the foreign procedures in lieu of those in the Common Rule.

Several international declarations have been formulated to address the involvement of human subjects in research. These are often cited in reference material submitted by foreign institutions and are provided for your information as enclosures. The first attempt to set international standards was the Nuremberg Code of 1947. This was an outgrowth of the Nuremberg Trials of war criminals who performed experiments on prisoners and detainees during the Second World War. The Nuremberg Code was followed in 1964 by the Declaration of Helsinki, which was itself revised several times by the World Medical Assembly. The most recent internationally recognized document is the Proposed International Guidelines for Biomedical Research Involving Human Subjects, which was produced in 1982 as a joint project of the World Health Organization and the Council for International Organizations of Medical Sciences (CIOMS). This document is currently under revision. Another important historical document in the U.S. is the Belmont Report - Ethical Principles and Guidelines for the Protection of Human Subjects of Research, produced by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979.

Each of these documents contain many laudable policies and principles, and are commendable efforts in the evolution of the concept of human subjects protections. It is important to note, however, that while some international codes contain laudable policies and principles, including ethical review by an appropriate review committee, informed consent and meaningful risk/benefit assessment, none to date lays out well a mechanism to implement them. Accordingly, a mechanism needs to be found to supplement international codes to implement these essential principles. It is necessary, therefore, to begin negotiations with foreign collaborators to supplement international codes to meet requirements of the Common Rule. Careful review is necessary to make certain that procedural requirements under the Common Rule are met and research can go forward.

The enclosed "Points to Consider" provide a framework in which appropriate evaluation of research proposals submitted by foreign governments and institutions can be accomplished. The Common Rule requires that entities that receive Federal support to conduct research involving human subjects provide an Assurance document that specifies how the provisions of the Common Rule will be implemented. Enclosed is a sample "Assurance of Protection for Human Subjects" as

a model document for foreign governments or institutions involved in research supported by the Department or Agency. This document contains all the essential elements required by the Common Rule and can be used as written to assure acceptable procedures. Many institutions will choose to base their Assurance on this sample document; however, should the institution prefer to develop its own Assurance document, the sample document may be used for a point by point comparison with the locally-developed document to determine the areas needing further discussion, negotiation, revision or exemption. Also enclosed is a "Narrative Format" that alternatively could be used as the basis for preparing an assurance document.

It is important to recognize that the requirements of the Common Rule are minimum standards. The issue of protection of human subjects is one that can not be entirely categorized and addressed by regulations. The principles set down by the policy must be taken into consideration in light of the culture and best interests of the subject. While exemption from certain requirements of the Common Rule may decrease the cost, difficulty, political or social complexity of performing a study, these considerations do not offer sufficient justification to waive protections afforded the subject.

Although it will be the rare exception, circumstances may exist wherein the best interests of the subject are served by waiver of one or more of the requirements of the Common Rule. Procedures for granting such a waiver must be established by each Department or Agency adopting the Common Rule. The Working Group on International Issues of the Human Subjects Research Subcommittee of the Committee on Life Sciences and *Health*, Federal Coordinating Council on Science Engineering and Technology, is available to Departments and Agencies to provide consultation concerning the waiver and other interpretation of Federal law and regulation in the area of protections of human subjects. The Working Group will offer recommendations to responsible officials regarding any issues or questions that arise in this evolving and complex area. It is important to note that the recommendations of the Working Group are advisory in nature and neither limit nor usurp the authority or responsibility of Department or Agency officials as designated in the Common Rule. Contact the Human Subjects Research Subcommittee Member, Roger Cortesi 202-564-6852 to initiate this process.

Enclosures:

1. "Points to Consider" - Common Rule
2. Sample "Assurance of Protection for Human Subjects in International Research"
3. "Narrative Format for Providing an Assurance in International Research"

12/92

FOR UNITED STATES DEPARTMENT AND AGENCY STAFF USE
Points to Consider
Protection of Human Subjects
International Research

A. Are Human Subjects Involved?

1. Does the proposed research provide a detailed description of the involvement of human subjects? What are the characteristics of the subject population, including the anticipated age range and health status? What is the gender and racial/ethnic composition? Are fetuses, pregnant women, children, prisoners, institutionalized or other vulnerable persons involved?

2. Are data about living, identifiable individuals involved in the form of specimens, records, or other data? [See Sec.102(f) Common Rule]

3. What are the potential physical, psychological, social, legal or other risks? What is the likelihood of these risks occurring?

4. Are there alternative treatments?

5. What procedures are there to minimize risks, including confidentiality? What kind of medical or professional interaction is available in the case of adverse effects to subjects? Are there methods to monitor data collected to ensure safety of participants?

6. Are the risks to subjects reasonable in relation to anticipated benefits to subjects and to knowledge expected to result from the research?

B. Is the Research Exempt? See the exempt categories in Sec.101(b)(l-6) of the Common Rule.

C. Institutional Review Board (IRB)

1. Is there a domestic institutional review board that will review the research?

and/or

Is there a local group that can meet the criteria and
perform the functions of an institutional review board?
If so, where is it located?

2. Who are the members? Can the membership criteria in Sec.107 of the Common Rule be fulfilled?

3. Are there any conflicts of interest? E.g. the investigator(s) must not be a member for purposes of his/her research, vote, or be present during IRB proceedings except to present his/her research and to answer questions. Family members of the investigator(s) must not be members, and so on.

4. Does/will the *IRB* assess -

   - Risks to subjects and how they can be minimized?
   - Risk/benefit ratio?
   - Equitable selection of subjects?
   - Informed consent process, context and documentation?
   - Confidentiality?
   - Special protections for vulnerable subjects?

5. Does/will the board meet as often as needed and at least annually?

6. Does/will the board keep minutes and records? (Sec. 115)

7. Does the board have sufficient autonomy and authority ~ be able to disapprove a protocol or to take action to suspend or terminate a protocol? (Sec.113)

D. Reporting [Sec.103(b)(5)]

1. How will the research institution report to the Department or Agency (and to the IRB) unanticipated problems involving risks to human subjects, instances of serious noncompliance or suspension or termination of IRB approval?

E. Informed Consent

1. What is the process to inform subjects about the study?

2. Are all the elements of informed consent included in the process? [Sec.116(a)] If not, why not?

3. Is there any exculpatory language. . .? [Sec.116]

4. Will a short form or long form be used? [Sec.117(a) (b)]

5. Where will documents be kept (if applicable)?

6. Is there a provision to give each participant an informed consent document (if applicable)? [Sec. 117(c))

7. If informed consent or parts of it are waived, can this be justified? i.e., is the study minimal risk? and will a waiver or alteration affect the rights and/or welfare of the subjects? and could the research not be practicably carried out without alteration or waiver? , if appropriate, will subjects be provided with additional information after the study? [Sec.116(d)] Clinical research involving FDA regulated products must meet the requirements of 21 CFR Part 50, which does not include a waiver provision for informed consent.

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F. Documentation

Does/will the institution provide accurate documentation addressing the following?

1. A statement of principles governing protection of human subjects in the institution in protecting human subjects? [Sec.103(b) (1)]

2. The institutional review board and its membership? [Sec.103(b) (3)]

3. The procedures it will follow to conduct initial and continuing review and report findings and noncompliance, and review changes to the protocol? [Sec.103(b) (4)&(5)]

4. The name of the responsible official who will act for the institution in protecting human subjects?

G. Additional Considerations - Based on Experience in Implementation:

1. It is important to emphasize that human subjects protections are important during the initial formulation of research. Participants need to be aware that there are requirements for descriptions, analysis, review and documentation.

2. Situations which result in conflicts of interests on an IRB often arise when institutions assemble an IRB with the investigator(s) as a member. In addition, if the IRB is the same group that formulates and endorses the scientific approach for the proposed research, there is an inherent conflict of interest. This type of situation should be discussed during initial discussions with foreign collaborators.

3. Informed consent procedures do allow some flexibility in documentation and information given, but justifications for flexibility must be carefully delineated.

4. Permission from community and/or tribal leaders may be necessary for the success of the project, but it must not substitute for individual informed consent. Waiver of individual consent may be made if conditions in Sec.116 are met and approved by the IRB.

H. Food and Drug Administration - Regulated Products

Does the research involve an FDA - regulated product?
(drug; biologic; device; food additive or color; radiation - emitting device)

1. Is the research covered by an Investigational New Drug Application (IND) or Investigational Device Exemption
(IDE)?

   If so, the FDA informed consent and IRB requirements (21 CFR 50 and 21 CFR 56) must be met. Please note that the FDA regulations do not provide for exempt -categories of research.

2. If the research is not covered by an IND, is the research being conducted in accordance with ethical principles of protecting the rights and welfare of the subject, that either meet or surpass the standards of the Declaration of Helsinki, amended 1989? (If the ethical standards of the country in which the research was conducted are used, the applicant must state in detail any differences between the standards and the
   - Declaration of Helsinki and explain why they offer greater protection to the human subjects.) [21 CFR Part 312.20] -[2l CFR Part 814.14.]

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(NAME OF INSTITUTION)

**ASSURANCE OF PROTECTION FOR HUMAN SUBJECTS
IN INTERNATIONAL RESEARCH**

(Name of Institution), hereinafter known as the "institution," hereby gives assurance that it will comply with the principles and procedures for protecting human research subjects specified below.

**PART 1
ETHICAL PRINCIPLES AND INSTITUTIONAL POLICIES GOVERNING
RESEARCH INVOLVING HUMAN SUBJECTS**

I. Ethical Principles Governing Human Subjects Research

This institution is guided by the ethical principles regarding research involving human subjects set forth in the _____ . These ethical principles guide the institution in the conduct of all its human subjects research.

NOTE In the blank Section above, the Institution may choose to cite the Belmont Report, the Declaration of Helsinki, or another appropriate code, declaration, or statement of principles that is consistent with the terms of this Assurance.

II. Institutional Policies Governing Human Subjects Research

A. This institution acknowledges and accepts its responsibilities for protecting the rights and welfare of all human subjects involved in the research which it sponsors or conducts.

B. This institution encourages and promotes an institutional atmosphere that safeguards the rights and welfare of human subjects.

C. It is the policy of this institution that before human subjects are involved in research which it sponsors or conducts, proper consideration must be given to:

(1) the risks to the subjects,
(2) the anticipated benefits to the subjects and others,
(3) the importance of the knowledge that may reasonably be expected to result, and
(4) the informed consent process to be employed.

D. Whenever appropriate, it is the policy of this institution to consider special safeguards for protecting research subjects who may be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

PART 2
HUMAN SUBJECT PROTECTIONS FOR RESEARCH
SUPPORTED BY THE UNITED STATES GOVERNMENT

I. Applicability

Part 2 of this Assurance applies only to the following research project which is conducted or sponsored by this institution and supported by the United States Government:

Project title _____

Project number _____

Project Investigator/Director _____

II. Institutional Responsibilities

A. This institution recognizes that all human subjects research supported by the United States Government, including the project referenced above, must be conducted in accordance with the United States Federal Policy for the Protection of Human Research Subjects.

B. The Institutional Review Board (IRB) listed in Attachment A has been designated to be responsible for the initial and continuing review of the project referenced above. The IRB includes at least five persons, including at least one scientist, one nonscientist, and one person not otherwise affiliated with the institution. Every nondiscriminatory effort has been made to include both women and men. The IRB also includes persons who are sensitive to the concerns of the populations from which subjects will be recruited.

C. Provisions have been made to provide both meeting space for the IRB and sufficient staff to support the IRB's review and record keeping duties.

III. IRB Responsibilities

A. The project referenced above has been and will be reviewed at convened meetings at which a majority of IRB members are present. A majority vote of those members present at the meeting is required for approval. The research investigators and their family members may not participate in IRB proceedings except to provide information requested by the IRB.

B. The IRB used the following criteria to determine that protections for human research subjects in this project are adequate:

(1) Risks to subjects are minimized.
(2) Risks to subjects are reasonable in relation to anticipated benefits.
(3) Selection of subjects is equitable.

(4) When appropriate, the data collected will be monitored during the course of the study to ensure safety of subjects.
(5) Privacy of subjects and confidentiality of data are protected.

C. The IRB has determined that legally effective informed consent will be obtained under circumstances that provide sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. Copies of all informed consent documents for this project are provided at Attachment B.

D. The IRB will review, and have the authority to approve, require modification in, or disapprove project changes.

E. Continuing reviews by the IRB will be conducted at intervals appropriate to the degree of risk, but not less than once per year. The IRB may be called into an interim review session by the Chairperson at the request of any IRB member or Institutional Official to consider any matter concerned with the rights and welfare of any subject.

F. The IRB will maintain documentation of its activities to include copies of research protocols, minutes of IRB meetings and continuing review records, correspondence with investigators, IRB membership with degrees and affiliations, IRB operating procedures, and statements of new findings provided to subjects. This documentation will be retained for at least three years after the completion of the project and will be accessible for inspection and copying by the supporting United States Government Agency.

G. The IRB will report promptly to appropriate institutional officials and to the supporting United States Government Agency

(1) any unanticipated problems or injuries involving risks to subjects or others,
(2) any serious or continuing noncompliance with this Assurance or with the requirements or determinations of the IRB,
(3) any changes in this project which are reviewed and approved by the IRB, and
(4) any suspension or termination of IRB approval.

IV. Responsibilities of Project Investigators/Directors

A. Project investigators/directors accept their responsibility to comply with the stipulations of the IRB and with the terms of this Assurance.

B. Project investigators/directors will report promptly to the IRB proposed changes in this project, and changes will not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the subjects.

C. Project investigators/directors will report promptly to the IRB any unanticipated problems or injuries involving risks to subjects or others.

PART 3
INSTITUTIONAL ENDORSEMENT AND CERTIFICATION

Project title _____

Project number _____

Project Investigator/Director _____

Date of IRB Approval _____

The officials signing below assure that the project referenced above was approved by the IRB on the date indicated and that the project will be conducted in accordance with all provisions of this Assurance and of the United States Federal Policy for the Protection of Human Research Subjects.

I. Authorized Official of the Institution Providing This Assurance

Signature

Name
Title
Address

Telephone

Date

II. Authorized Official of the Institution with the IRB
([nclude **only** if different *from* the institution above)

This institution authorizes the designation of its IRB for review of the project referenced in this Assurance.
Signature Date

Name
Title
Address
Telephone

III. IRB Chairperson
Signature Date
Name
Title
Address

Telephone

IV. Local Principal Investigator

Signature

Name
Title
Address

Telephone

Date

PART 4
AGENCY APPROVAL

All parts of this Assurance are in compliance with the requirements of the Federal Policy for the Protection of Human Research Subjects.

Agency Approving Official
Signature Date
Title
Name
Address

Telephone

ASSURANCE NUMBER:

[Note: The period for which this document is approved should be defined in accordance with each Department's or Agency's policies.

Revised 06/06/96

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(PLEASE RESUBMIT AS CHANGES OCCUR)

INSTITUTIONAL REVIEW BOARD (IRB) MEMBERSHIP DATE: _____

NAME OF INSTITUTION PROVIDING THIS ASSURANCE _____ ASSURANCE NO: _____

NAME OF INSTITUTION WITH THE IRB (if different from above) _____ ASSURANCE NO: _____

MEMBER NAME FIRST M.I. LAST	HIGHEST DEGREES EARNED	PRIMARY SCIENTIFIC OR NONSCIENTIFIC SPECIALITY	AFFILIATION WITH INSTITUTION(S) ABOVE (YES/NO; IF YES, WHICH ONE)	ADDRESS AND PHONE NUMBER FOR CHAIRPERSON ONLY
				SIGNATURE: IRB CHAIR _____ Note: Each IRB shall include at least one member with one member who is not otherwise affiliated with this institution. Please review 45 FR 46.107 for other IRB membership requirements.

ATTACHMENT B

INFORMED CONSENT DOCUMENT(s)

Attach copies of all IRB-approved Informed Consent Documents to be used in the projects referenced in the Assurance.

Revised 6/12/96

Narrative Format for Providing An
Assurance for International Research

1. Please describe what principles govern your institution that address protecting the rights and welfare of human subjects of research (e.g. Declaration of Helsinki, Council of International Organizations of Medical Sciences Proposed Guidelines).

2. Please describe the institutional review board (IRB - group *to protect human subjects) in your institution* which *can act* to review this protocol to protect human subjects? The IRB must be able to address the following concerns: Minimizing risks to participants; risks to participants and benefits to participants and others; fair selection of participants; special protections for vulnerable participants; informed consent of participants and how this will be documented; monitoring data for safety; confidentiality of data.

3. Please describe the membership of the IRB. Who serves as chairperson? Who are the members? What are their educational degrees and affiliations? (The IRB should include at least five persons; at least one unaffiliated with the institution; one scientist; one non-scientist; both men and women; someone with expertise about the research and who knows about the community(ies) from which participants will be drawn.) Note that the principal investigator or family members will not be part of the IRB proceeding or vote.

4. Please describe how the IRB will conduct its initial and continuing review and how the IRB will be informed promptly of any changes contemplated in the protocol.

5. Please describe the informed consent process and provide the document(s) to be used to advise participants about the research and seek their Consent. [List items from Sec.116]

   If informed consent is not obtained via a written document, please describe how the consent will be obtained. There must be a witness to the oral presentation to sign the document containing the information presented to the participant.

   If informed consent is not sought or all the elements are not addressed, please indicate the conditions that the IRB cites that are appropriate to justify waiving as described in Sec.116.

6. Please describe how you will maintain the records (copies of research protocols; minutes; review records; correspondence; IRBL membership, with degrees and affiliations; procedures; statements of new findings to give to participants).

7. Please describe how the IRB, your institution, and this Department will be informed of any serious or continuing noncompliance with human subjects protections or if the IRB has suspended or withdrawn its approval.

8. Please provide the signature of the institutional official responsible for this project and for making sure that human subjects are protected.