U.S. Department of Energy
Washington, D.C.

ORDER

DOE O 443.1A

Approved: 12-20-07

SUBJECT: PROTECTION OF HUMAN SUBJECTS

1. OBJECTIVE. To establish Department of Energy (DOE) procedures and responsibilities for implementing the policy and requirements set forth in 10 Code of Federal Regulations (CFR) Part 745, Protection of Human Subjects; and in DOE P 443.1A, *Protection of Human Subjects*, dated 12-20-07.

2. CANCELLATION. This Order cancels DOE Order 443.1, *Protection of Human Subjects*, dated 5-15-00. Cancellation of an Order does not by itself modify or otherwise affect any contractual obligation to comply with the Order. Contractor Requirements Documents (CRDs) containing directive requirements that have been applied to a contract remain in effect until the contract is modified to eliminate or replace requirements from canceled directives.

3. APPLICABILITY.

   a. DOE Elements. Except for exclusions in paragraph 3d, this Order applies to all Departmental elements, including those created after the Order is issued. (Go to http://www.directives.doe.gov for the current listing of Departmental elements.)

      The National Nuclear Security Administration (NNSA) Administrator will assure that NNSA employees and contractors comply with their respective responsibilities under this directive. Nothing in this Order will be construed to interfere with the NNSA Administrator's authority under Section 3212(d) of Public Law (P.L.) 106-65 to establish Administration-specific policies, unless disapproved by the Secretary.

   b. DOE Contractors. Except for the exclusions in paragraph 3d, the requirements of the Contractor Requirements Document (CRD), Attachment 1, sets forth the requirements of this Order that will apply to contracts that include the CRD. The CRD must be included in contracts for the management or operation of a DOE-owned or -leased facility that involves human subjects research (HSR) as defined in paragraph 6.e., and comprehensively explained in DOE P 443.1A, irrespective of the party conducting the HSR under the contract.

   c. Other Contracts and Agreements. Refer to paragraph 5e(3).

   d. Exclusions. Bonneville Power Administration.

4. REQUIREMENTS.

   a. Approvals. No HSR conducted with DOE funding, at DOE institutions, or by DOE personnel may be initiated without both a Federalwide Assurance (FWA) and approval by the cognizant Institutional Review Board (IRB) in accordance with 10 CFR 745.103.

b. Solicitations. Any solicitation for research involving human subjects must indicate the applicable requirements of this Order, 10 CFR 745, and 45 CFR 46.

c. Contracts and Agreements. Any DOE contract, financial assistance agreement, or other agreement involving HSR must prescribe compliance with this Order, 10 CFR 745, and 45 CFR 46. See also CRD (Attachment 1).

d. Notification. The HSR Program Manager (and when an NNSA element is involved, the NNSA HSR Manager) must be notified in writing and within a reasonable time of any new solicitation or proposal involving HSR (including personally identifiable information or materials) that addresses:

(1) an institution without an established IRB;

(2) a foreign country;

(3) a potential for significant controversy (e.g., negative press or reaction from stakeholder or oversight groups);

(4) research subjects in a protected class; or

(5) the generation or use of classified or unclassified controlled information.

e. Reporting.

(1) HSR projects must be reported annually to the HSR Projects Database in accordance with directions and schedules provided by the HSR Program Manager.

(2) The HSR Program Manager will be notified in writing and within a reasonable time of:

(a) significant adverse events, unanticipated risks, and complaints about the research, with a description of corrective actions taken and/or to be taken;

(b) suspension or termination of IRB approval of research; and

(c) known or potential incidents of noncompliance with requirements of this Order, 10 CFR 745, 45 CFR 46, and any approved plan for correcting a noncompliance.

f. Waivers. Requests for waivers from the requirements of 10 CFR 745 or this Order must be submitted to the HSR Program Manager (and when an NNSA element is involved, the NNSA HSR Manager) in writing. A waiver may be recommended by the HSR Program Manager (or by the NNSA HSR Manager when an NNSA element is involved) to the Secretary or the Secretary's designee.

Waiver decisions must set forth in writing the basis for granting or denying the request.

g. Protected Classes. Research involving fetuses, pregnant women, and in vitro fertilization; prisoners; or children must be conducted in accordance with 45 CFR 46 Subparts B, C, and D.

5. RESPONSIBILITIES.

a. Under Secretary for Science.

(1) Monitors implementation of 10 CFR 745 within the Department in accordance with policy established by the Secretary and DOE P 443.1A in consultation with the NNSA, as appropriate.

(2) Determines what constitutes Departmental-related HSR, in consultation with the NNSA.

(3) Ensures implementation of human research subject protection measures in accordance with the requirements of this Order and 10 CFR 745 in consultation with the NNSA HSR, as appropriate.

(4) Designates the HSR Program Manager. For DOE, the HSR Program Manager resides within the SC Office of Biological and Environmental Research.

b. Under Secretary for Nuclear Security and Administrator of the National Nuclear Security Administration designates the NNSA HSR Manager.

c. DOE HSR Program Manager.

(1) Develops procedures for the HSR program in consultation with the NNSA HSR Manager, as appropriate.

(2) Prepares and updates guidance to be followed for obtaining approval for HSR in consultation with the NNSA HSR Manager, as appropriate.

(3) Reviews/approves (or when an NNSA element is involved, reviews and may recommend approval of) local plans to correct any noncompliance with applicable HSR requirements, or to mitigate adverse study events.

(4) Provides advice and guidance on evolving Departmental and national bioethics and regulatory issues regarding human research subjects protection and helps identify and resolve program/project concerns in consultation with the NNSA HSR Manager, as appropriate.

(5) Develops and conducts educational programs on bioethics and human research subjects protection requirements, practices, and procedures

relevant to DOE employees, DOE contractor personnel, financial assistance recipients, and the public in consultation with the NNSA HSR Manager, as appropriate.

(6) Regularly conducts institutional performance reviews to assess compliance with human research subjects protection requirements in consultation with the NNSA HSR Manager, as appropriate.

(7) Serves as the Chair of the DOE Human Subjects Working Group and as the official DOE representative to groups with bioethics and HSR interests. The NNSA HSR Manager shall be invited to attend all such meetings.

(8) Makes recommendations to the Secretary or the Secretary's designee regarding requests for waivers to requirements of 10 CFR 745.101 and satisfies the advance notice and publication requirements of 10 CFR 745.101(i) prior to the granting of any waiver (in consultation with the NNSA HSR Manager, as appropriate).

(9) Concurs in HSR provisions in interagency agreements in consultation with the NNSA HSR Manager, as appropriate.

(10) Maintains the HSR Projects Database for the Department.

d. NNSA HSR Manager.

(1) When an NNSA element is involved, reviews requests for waivers to requirements of 10 CFR 745 and makes recommendations to the Secretary through the NNSA Administrator. Ensures that the advance notice and publication requirements of 10 CFR 745.101(i) are met prior to the granting of any waiver.

(2) Works with the HSR Program Manager, as outlined in paragraph 5c of this Order.

e. Secretarial Officers or their Designees. Note: Per DOE M 251.1-1B and as used throughout this Order, the term "Secretarial Officer" refers to the Secretary, Deputy Secretary, the Under Secretaries, and the Assistant Secretaries and Program Office Directors reporting to the Secretary either directly or through the Deputy Secretary or Under Secretaries. The NNSA Administrator and Deputy Administrators are Secretarial Officers.

(1) Ensure that all proposals for research, studies, tests, surveys, surveillance, or other data collection are reviewed to identify research involving human subjects.

(2) Ensure that any questions or uncertainties regarding the applicability of human research subjects protection requirements to such proposals, and any other issues and concerns regarding the requirements of this Order, are

promptly referred to the HSR Program Manager for resolution (or the NNSA HSR Manager when an NNSA element is involved).

(3) Ensure that the contracting officer is advised when work statements for proposed agreements include HSR. The requirements of this Order will be applied to HSR conducted with DOE funding, at DOE institutions, or by DOE personnel under agreements other than site/facility management contracts, such as support services contracts, grants, cooperative agreements, work-for-others agreements, and interagency agreements.

(4) Ensure their staffs and subordinate field elements comply with the requirements of this Order, including the notification requirements in paragraph 4e.

(5) Actively participate in human research subjects protection educational programs.

(6) Assure self-assessments are periodically conducted to verify compliance with the requirements of this Order.

(7) At their discretion, conduct further review and approve or disapprove research that has been approved by the IRB. (Note: Secretarial Officers or their designees may not approve HSR that has not been approved by an IRB. See 10 CFR 745.112.)

(8) Ensure appropriate oversight of the administration of research subjects protection programs of contractors and financial assistance recipients under their cognizance, and other parties to DOE agreements, to ensure compliance with applicable human research subjects protection requirements.

(9) Ensure that the HSR Program Manager and the NNSA HSR Manager are involved in negotiating those portions of interagency agreements that address HSR.

(10) Appoint a point of contact for interacting with the HSR Program Manager (and/or NNSA HSR Manager, when an NNSA element is involved) on program-related and/or Department-wide issues.

6. DEFINITIONS.

a. Assurance. The written documentation, satisfactory to the Secretary of Energy, required from the prospective performing institution, that ensures institutional compliance with and implementation of DOE and Department of Health and Human Services (DHHS) regulations for the protection of human research subjects. The only documentation currently meeting this requirement is a Federalwide

Assurance (FWA). See http://www.hhs.gov/ohrp/assurances/assurances_index.html.

b. Adverse Effect. . A direct result of an administered research protocol (e.g., negative or deleterious drug reaction, collateral damage to the human subject).

c. Adverse Event. A result surrounding or indirectly related to the entire research process (e.g., mishaps, mistakes, incorrect dosage administered, reconsideration of human subject involvement).

d. DOE HSR Projects Database. A compilation of summary information, which is available on the website at: http://hsrd.orau.gov/, updated annually, on every HSR non-exempt project funded by DOE, conducted at DOE institutions or facilities, or performed with DOE or contractor personnel.

e. Human Subjects Research (HSR). Any systematic investigation (including research development, testing, and evaluation) utilizing living individuals or personally identifiable information or materials, designed to develop or contribute to general knowledge. See DOE P 443.1A for examples and exclusions.

f. Human Subjects Research Program Manager (HSR Program Manager). The DOE HSR Program Manager (SC23.2) designated by the Under Secretary for Science.

g. NNSA Human Subjects Protection Designee (NNSA HSR Manager). The NNSA HSR Manager designated by the NNSA Administrator and Under Secretary for Nuclear Security.

h. Institution. Any public or private entity or agency (including Federal, State, and other agencies). This term refers to laboratories and other facilities managed by DOE, DOE contractors, or DOE financial assistance recipients.

i. Institutional Review Board (IRB). A committee or board established by an institution that performs initial and continuing reviews of research involving human subjects, and is registered with the Office for Human Research Protections (OHRP) and designated on an FWA.

7. REFERENCES.

a. *DOE Human Subjects Protection Resource Book*, Office of Biological and Environmental Research, 2007.

b. DOE O 241.1A Chg 1**,** *Scientific and Technical Information Management*, dated 10-14-03, which establishes Department of Energy (DOE) requirements and responsibilities to ensure that scientific and technical information (STI) is identified, processed, disseminated, and preserved in a manner that (a) enables the scientific community and the public to locate and use the unclassified and unlimited STI resulting from DOE's research and related endeavors and (b) ensures

access to classified and unclassified controlled STI is protected according to legal or Departmental requirements.

c. DOE O 412.1A, *Work Authorization System*, dated 4-21-05, which provides the policy, responsibilities, and procedures for authorizing and administering DOE-funded work performed under DOE contracts.

d. DOE P 443.1A, *Protection of Human Subjects*, dated 12-20-07, which defines DOE policy for the protection of human subjects in research activities.

e. DOE O 481.1C, *Work for Others (Non--Department of Energy Funded Work)*, dated 1-24-05, which establishes the policy, responsibilities, and procedures for authorizing and administering work for non-DOE entities by DOE/National Nuclear Security Administration (NNSA) and/or their respective contractor personnel or the use of DOE/NNSA facilities that is not directly funded by DOE appropriations.

f. DOE M 481.1-1A Chg 1, *Reimbursable Work for Non-Federal Sponsors Process Manual*, dated 9-28-01, provides detailed requirements to supplement DOE O 481.1C, Work For Others (Non-Department of Energy Funded Work), dated 1-24-05, which establishes requirements for the performance of work for non-DOE/non-NNSA entities by DOE/NNSA/contractor personnel and/or the use of DOE/NNSA facilities that is not directly funded by DOE/NNSA appropriations.

g. DOE M 483.1-1, *DOE Cooperative Research and Development Agreements Manual*, dated 1-12-01, which provides detailed requirements to supplement DOE O 483.1, DOE Cooperative Research and Development Agreements, dated 1-12-01, which establishes requirements for the performance of technology transfer through the use of Cooperative Research and Development Agreements (CRADAs).

h. DOE O 484.1, *Reimbursable Work for the Department of Homeland Security*, dated 8-17-06. The Order establishes DOE policies and procedures for the acceptance, performance, and administration of reimbursable work directly funded by the Department of Homeland Security.

i. 10 CFR 600, *DOE Financial Assistance Rules*, which provides the policies and procedures for administration and management of all DOE financial assistance activities.

j. 10 CFR 602, *Epidemiology and Other Health Studies Financial Assistance Program*, which sets forth the policies and procedures applicable to the award and administration of financial assistance agreements and cooperative agreements for health--related research, education/training, conferences, communication, and related activities.

k. 10 CFR 605, *Office of Science Financial Assistance Program*, as explained at doe.gov/grants/605index.html, which provides policies and procedures for the administration and management of basic and applied research financial award agreements awarded by the Office of Science.

l. 10 CFR 745, *Protection of Human Subjects*, which sets out Federal requirements for DOE for the protection of human subjects involved in research activities.

m. 10 CFR 1008**,** *Records Maintained On Individuals (Privacy Act)* which establishes the procedures to implement the *Privacy Act of 1974* (PL. 93-579, 5 U.S.C. 552a) within the Department of Energy.

n. 45 CFR 46, *Protection of Human Subjects, Subparts B, C, and D*, which sets out DOE prescribed DHHS requirements for protected classes of human research subjects.

o. The *National Nuclear Security Administration Act*, Title 32, Pub. L No. 106-65, as amended.

p. 5 United States Code 552, The *Freedom of Information Act* (Public Law 89-487 as amended), which establishes the right of citizens to request information from Federal agencies and establishes a framework of procedures to implement this right.

8. NECESSITY FINDINGS STATEMENT. In compliance with statutory requirements in Sec. 3174, P.L. 104-201 (50 U.S.C. 2584 note), DOE hereby finds that the subject Order is necessary for the protection of human research subjects within the DOE community.

9. CONTACT. Questions regarding this Order should be addressed to the DOE Program Manager, HSR Program, at the Office of Science (SC23.2), telephone 301-903-3213, or the NNSA human subjects protection designee, as appropriate. Information about the DOE HSR protection program may be found at http://humansubjects.energy.gov/.

BY ORDER OF THE SECRETARY OF ENERGY:

CLAY SELL
Deputy Secretary

CONTRACTOR REQUIREMENTS DOCUMENT
DOE O 443.1A, *PROTECTION OF HUMAN SUBJECTS*

Regardless of the performer of the work, the contractor is responsible for compliance with the requirements of this CRD. The contractor is responsible for flowing down the requirements of this CRD to subcontracts at any tier to the extent necessary to ensure the contractor's compliance with the requirements.

As directed by the contracting officer, the contractor must—

Note: Throughout this CRD, the term "Human Subjects Research Manager (HSR Manager)" refers either to the DOE HSR Manager (SC23.2) or to the NNSA human subjects protection designee except where otherwise noted.

1. Ensure that the HSR Program Manager (and, when an NNSA element is involved, the NNSA HSR Manager) is notified of any new HSR project involving:

   a. an institution without an established Institutional Review Board (IRB);

   b. a foreign country;

   c. the potential for significant controversy (e.g., negative press or reaction from stakeholder or oversight groups);

   d. research subjects in a protected class; or

   e. the generation or use of classified or unclassified controlled information.

2. Ensure that research involving human subjects conducted at the contractor-operated institution, with the contractor's DOE-contract funding, or by contractor personnel is conducted in accordance with applicable requirements. (See 10 CFR 745 and 45 CFR 46.)

3. Ensure that contractor-issued solicitations or proposals for research, studies, tests, surveys, surveillance, or other data collection are reviewed to identify research involving human subjects and that any resulting agreements include the substance of the requirements in this CRD.

4. Ensure that no research involving human subjects conducted at the contractor-operated institution, with the contractor's DOE-contract funding, or by contractor personnel is initiated without prior IRB approval under the terms of an approved assurance covering the research.

5. Submit an application for a Federalwide Assurance (FWA) to the Office of Human Research Protections with the Department of Health and Human Services (DHHS) and, once approved, maintain this FWA covering proposed and ongoing HSR. The FWA has been accepted by the Secretary of Energy as appropriate written documentation from the prospective performing institution that ensures institutional compliance with and

implementation of DOE and DHHS regulations for the protection of human research subjects. See http://www.hhs.gov/ohrp/assurances/assurances_index.html and/or contact the DOE HSR Protection Program, SC-23.2, telephone 301-903-3213, or the NNSA human subjects protection designee, as appropriate.

6. Ensure that research is reviewed at intervals appropriate to the degree of risk, but not less than once per year, to assess the risk to test subjects and to assure the risk is reasonable in relation to anticipated benefits.

7. Periodically conduct self-assessments to ensure compliance with the HSR Program procedures and other requirements.

8. Prepare and submit an annual report for the HSR Projects Database in accordance with directions and schedules provided by the HSR Program Manager and the contracting officer.

9. Report the following to the HSR Program Manager (and, when an NNSA element is involved, the NNSA HSR Manager):

   a. any significant adverse events, unanticipated risks; and complaints about the research, with a description of any corrective actions taken and/or to be taken;

   b. any suspension or termination of IRB approval of research;

   c. any significant non-compliance with HSR Program procedures or other requirements.

   NOTE: The adverse effects of any study are to be reported to the IRB for evaluation for further action with HSR Program Manager, (and, when an NNSA element is involved, the NNSA HSR Manager)

10 Submit requests for waivers from these requirements in writing through the contracting officer to the HSR Program Manager (and, when an NNSA element is involved, the NNSA HSR Manager) with appropriate justification.

11. Actively participate in HSR educational programs.