U.S. Department of Energy

Washington, D.C.

ORDER

DOE O 443.1D

Approved: 08-05-2026

SUBJECT: PROTECTION OF HUMAN RESEARCH SUBJECTS

1. PURPOSE. This Order establishes the United States (U.S.) Department of Energy (DOE) policy and principles for the protection of human subjects involved in DOE supported- or -conducted research. While human subjects research (HSR) provides important medical and scientific benefits to society, this directive outlines requirements for ensuring that the rights and welfare of research participants are prioritized. This Order outlines specific DOE procedures and responsibilities for implementing the requirements of 10 Code of Federal Regulations (CFR) Part 745, Protection of Human Subjects, 45 CFR Part 46, Protection of Human Subjects, and the 1997 Presidential Memorandum, Strengthened Protections for Human Subjects of Classified Research. It further details criteria for determining whether an activity involves human subjects and establishes the oversight process for research activities, including those exempted at 10 CFR § 745.104, Exempt research.

2. CANCELS/SUPERSEDES. This Order cancels DOE Order (O) 443.1C, Chg.1(LtdChg), *Protection of Human Research Subjects*, dated November 26, 2019.

   Cancellation of a directive does not, by itself, modify or otherwise affect any contractual or regulatory obligation to comply with the directive. Contractor Requirements Documents (CRDs) that have been incorporated into a contract remain in effect throughout the term of the contract unless and until the contract or regulatory commitment is modified to either eliminate requirements that are no longer applicable or substitute a new set of requirements.

3. APPLICABILITY.

   a. Departmental Applicability.

      (1) With the exception of the equivalencies/exemptions listed in Paragraph 3.c., this Order applies to all Departmental Elements.

      (2) The Administrator of National Nuclear Security Administration (NNSA) will assure that NNSA employees and contractors comply with their respective responsibilities under this directive. Nothing in this Order/Notice will be construed to interfere with the NNSA Administrator's authority under Section 3212(d) of Public Law (P.L.) 106-65, *National Defense Authorization Act for Fiscal Year 2000*, to establish Administration-specific policies, unless disapproved by the Secretary.

(3) In accordance with the responsibilities and authorities assigned by Executive Order (EO) 12344, Naval Nuclear Propulsion Program, codified at 50 U.S.C. Sections 2406, Deputy Administrator for Naval Reactors, and 2511, Naval Nuclear Propulsion Program, and to ensure consistency through the joint Navy/DOE Naval Nuclear Propulsion Program, the Deputy Administrator for Naval Reactors (Director) will implement and oversee requirements and practices pertaining to this directive for activities under the Director's cognizance, as deemed appropriate.

b. DOE Contractors and Parties to Other Agreements.

(1) DOE Management and Operating (M&O) contracts, including Department of Energy Acquisition Regulation (DEAR) 970.5204-2, Laws, regulations, and DOE directives, must include the CRD, Attachment 1, establishing the requirements applicable to DOE contractors when their scope may include research involving humans through interaction, intervention, or use of their data or specimens.

(2) Any DOE contract, financial assistance agreement, or other agreement for the conduct of research involving humans through interaction, intervention, or use of their data or specimens must require compliance with the requirements set forth in this Order or the CRD (Attachment 1), as well as with 10 CFR 745 and 45 CFR 46.

c. Exemptions.

(1) Requests for partial or full exemptions must be submitted in writing to the DOE Human Subjects Protection Program (HSPP). Exemptions will be recommended to the Secretary by the HSPP after concurrence by the DOE Institutional Official (IO). The basis for approval or denial must be documented in writing.

(2) Bonneville Power Administration is exempt from the requirements of this Order.

4. REQUIREMENTS.

a. HSR[1] conducted or supported by the DOE must be conducted in accordance with the principles outlined in the Belmont Report and all applicable federal,[2] DOE-specific, sponsor-specific, and other requirements, including 10 CFR 745, 45 CFR 46, and this Order.

(1) HSR must be conducted in accordance with 10 CFR 745.103; under a valid Federalwide Assurance (FWA) and only initiated after review and approval by an Institutional Review Board (IRB) as defined in this Order.

[1] As defined at 10 CFR § 745.102(e) and (l), respectively.
[2] Including applicable parts of 21 CFR Chapter 1 when activities are regulated by the FDA.

(2) HSR meeting the categories of exemption at 10 CFR 745.104 must have received a determination from an IRB, Human Subjects Protection (HSP) office, or their designee.

(3) Non-DOE-supported researchers who will conduct HSR at/using DOE/NNSA user facility capabilities must provide documentation of IRB or ethics board approval or exemption determination from their home institution. Such HSR is not otherwise required to comply with the provisions of this Order, unless the DOE/NNSA site hosting the user facility determines such compliance is necessary.

b. For DOE-supported or -conducted research involving humans through interaction, intervention, or use of their data or specimens, but that may not constitute HSR per 10 CFR 745.102(e) and (l), the following requirements still apply.

(1) Institutions must adopt a process under which an IRB, HSP office or their designee determines whether proposed research constitutes HSR for the purposes of this Order and the applicability of 10 CFR 745 and 45 CFR 46.

(2) Such determinations of whether a project constitutes HSR are required when research involves:

(a) The use of information or specimens for which the identity of the subject is or may readily be ascertained by the investigator or is linked or linkable to the information or specimens; or

(b) The study of humans in a systematically modified environment, defined as modification of the human environment in this Order; or

(c) Human terrain mapping (HTM) activities. Regardless of HSR determination, the following requirements apply to all HTM activities.

1 At DOE and all DOE sites, HTM must be limited to only activities involving the analysis and modeling of de-identified data.

2 Prior to initiation, statements of work for HTM projects must be submitted to the HSPP for DOE Headquarters review and approval. If the project is to be conducted by or for the intelligence community, such as through strategic partnership projects (SPPs) or the Strategic Intelligence Partnership Program (SIPP), DOE Office of Intelligence and Counterintelligence (DOE-IN) must also review and approve it prior to initiation.

c. Central DOE IRBs. DOE Headquarters supports two registered IRBs for review of DOE-supported or -conducted HSR; the Central DOE IRB and the Central DOE IRB-Classified (IRB-C).

(1) The applicable Central DOE IRB must serve as the reviewing IRB as follows:

(a) When HSR includes:

1 Targeted inclusion of DOE/NNSA federal employees, or employees from more than one DOE site, as subjects or the use of their data; or

2 Engagement of three or more DOE sites as study team members; or

3 Classified and unclassified intelligence and intelligence-related HSR, regardless of funding source (including, but not limited to, studies funded through SIPP, DOE-IN, or other DOE program offices using classified datasets).

(b) Exceptions to this requirement may be authorized in writing by the DOE HSPP; however, the IRB review conducted must still adhere to the requirements of this Order and 10 CFR 745.

(2) An unaffiliated member must be among the voting IRB members present in order for a DOE IRB to conduct business requiring full board review.

(3) Researchers who submit studies to the DOE site IRBs and members of these IRBs must complete initial and periodic refresher training in HSP.

(4) IRB records must be maintained and managed in accordance with applicable NARA-approved records schedules.

d. Considerations for HSR.

(1) DOE-Affiliated Personnel as Subjects. Targeted inclusion of DOE-affiliated personnel (defined in this Order) as participants, or use of their data or specimens, in HSR requires additional consideration to protect potentially vulnerable subjects. This HSR must be reported to the DOE Human Subjects Research Database (HSRD) as defined in paragraph 4.f.(2), below. Prior to initiation of HSR targeting DOE-affiliated personnel, researchers must obtain:

(a) Written approval from the HSP office of the single DOE site being targeted for inclusion, or

(b) Review and approval by the Central DOE IRB when DOE federal employees or more than one DOE site are targeted for inclusion, unless an exemption is provided in writing by the DOE HSPP.

(2) Personally Identifiable Information (PII). When DOE-supported or -conducted HSR includes the collection and/or use of PII, all applicable requirements of DOE O 206.1A, *DOE Privacy Program,* or current version, must be met. This includes safeguarding PII and reporting suspected or confirmed breaches, which are considered Unanticipated Problems, as defined in this Order.

(3) International HSR. DOE-supported or -conducted HSR, regardless of the location of the activity or participant, domestic or abroad, must adhere to the requirements of this Order. This policy, however, does not preempt any foreign laws or regulations[3] that may otherwise be applicable, as addressed in 10 CFR 745.101(g). Where differences in applicable standards exist, the requirements that are most protective of human subjects should be applied.

(4) Classified HSR.

(a) In addition to IRB approval, HSR that is classified, in whole or in part, must not be initiated without subsequent approval by the DOE IO. The DOE IO, in consultation with the HSPP, will determine whether to approve the project or brief the Secretary about the project prior to their decision.

(b) Informed consent may only be waived for classified HSR if the project meets one or more of the categories of exemption at 10 CFR 745.104. However, a full IRB review will still be required, as categorical exemption from the requirements of 10 CFR 745 and 45 CFR 46 is prohibited for classified HSR.

(c) The use of the expedited review process is prohibited. The fact that research falls into a particular expedited category may be noted, but a full IRB review will be required.

(d) The identity of the sponsoring federal agency must be disclosed to subjects unless the sponsor requests it not be done because it could compromise intelligence sources or methods. Additionally, the research must be no more than minimal risk, and the IRB must determine that not disclosing the identity will not adversely affect the subjects.

[3] In particular, state and international privacy law should be considered.

(e) The informed consent document will state that the project is classified, what that means for the purposes of that project, and to which part of the research that applies. The IRB must determine whether the potential human subjects need access to classified information to make a valid informed consent decision.

(f) When reviewing classified HSR, the unaffiliated member of a DOE or DOE site IRB must be a non-governmental member (not currently a federal employee or a DOE site contractor employee) with appropriate security clearance.

(g) Any IRB member has the right to appeal the IRB's decision to approve a project to the DOE IO, and if not resolved to the IRB member's satisfaction, the IRB member may advance the appeal to the Secretary of Energy. If still dissatisfied, the IRB member can appeal that approval decision to the Director of the Office of Science and Technology Policy (OSTP) or that Director's designee, or the Director of National Intelligence (ODNI), or that Director's designee. The Director of OSTP, or that Director's designee, or the ODNI, or that Director's designee, will review and approve or disapprove the research, or will convene or designate an IRB that is, to the extent possible, made up of unaffiliated members with the appropriate qualifications and clearance to approve or disapprove the research.

(h) All records related to IRB review/approval of classified HSR, as well as key researcher records, must be maintained permanently. During and following the completion of classified research, copies of all signed classified consent forms must be stored in a separate but secure central location (e.g., Security Policy office or IRB office), other than the researchers' office, and participants of such research must be notified during the consenting process regarding how to access a copy of their individual signed classified consent forms should they want to in the future.

e. Solicitations and Agreements.

(1) DOE-issued solicitations or proposals for the conduct of research involving humans through interaction, intervention, or use of their data or specimens must require compliance with this Order, 10 CFR 745, and 45 CFR 46.

(2) DOE-issued contracts, financial assistance agreements, and all other agreements for the conduct of research involving humans through interaction, intervention, or use of their data or specimens must require compliance with this Order, 10 CFR 745, and 45 CFR 46.

f. Required Reporting.

(1) Prompt notification[4] to the DOE HSPP is required when any of the following occur during performance of DOE-supported or conducted HSR, including projects determined to meet a category of exemption at 10 CFR 745.104.

(a) Unanticipated Problems[5] involving risks to subjects or others.

(b) Serious or continuing noncompliance with this Order, 10 CFR 745, 45 CFR 46, or the requirements or determinations of the IRB.

(c) Suspension or termination of IRB approval.

(2) Human Subjects Research Database Reporting. All DOE-supported and -conducted HSR, including those projects determined to meet a category of exemption at 10 CFR 745.104, and HSR that targets DOE-affiliated personnel, must be reported to the HSRD as follows:

(a) Project-specific information, as indicated by the HSPP, must be provided after initial IRB approval or determination of exemption has been obtained.

(b) Updated project-specific information must be provided every 3 years, or when substantive changes occur, such as any change impacting HSRD reporting categories, study objectives, or upon study completion.

(c) In cases where a DOE Headquarters program office funds outside institutions to conduct HSR, the program office will be responsible for ensuring HSRD reporting requirements are met.

5. RESPONSIBILITIES.

All DOE employees, contractors, financial assistance recipients, and other parties to DOE research share responsibility for protecting the rights and welfare of human subjects.

a. The Secretary of Energy.

(1) Responsible for oversight of DOE-supported and conducted HSR. Delegate this responsibility to a Senior DOE IO for HSR. For DOE, the IO is at the Senior Executive Service (SES) level from the Biological and Environmental Research (BER) program.

[4] Defined in Attachment 2 of this Order.
[5] Defined in this Order to include adverse events and data breaches.

(2) Approve, or defer to the DOE IO to approve, requests for partial or full exemptions from the requirements of this Order when deemed appropriate by the DOE IO and the DOE HSPP.

(3) If IRB member appeals are elevated to the Secretary of Energy, review and adjudicate IRB member appeals of IRB approval determinations for classified projects.

b. Under Secretary for Science.

(1) Monitor compliance with this Order, 10 CFR 745, and 45 CFR 46, within DOE in accordance with policy established by the Secretary and in consultation with NNSA, as appropriate.

(2) Designate the DOE IO and the DOE HSP Program Manager.

(3) Delegate review and approval of statements of work for HTM projects submitted by DOE's non-NNSA sites to the DOE HSP Program Manager.

c. Under Secretary for Nuclear Security and National Nuclear Security Administration.

(1) Designate the NNSA HSP Program Manager.

(2) Delegate review and approval of statements of work for HTM projects submitted by DOE's NNSA sites to the NNSA HSP Program Manager.

(3) In consultation with the Under Secretary for Science and Innovation, monitor compliance with this Order.

d. The DOE Institutional Official.

(1) Reside within DOE Office of Science (DOE-SC) and serves at the SES level from BER.

(2) Serve as the Senior DOE official responsible for overseeing the Departmental implementation of the requirements of this Order, 10 CFR 745, 45 CFR 46, and related EOs, Presidential Memoranda, and other Presidential directives and international requirements, as applicable, in consultation with the NNSA, as appropriate.

(3) Report to the Secretary of Energy for purposes of this function and determine what constitutes Departmental HSR, in consultation with the NNSA.

(4) Allocate resources for the DOE HSPP and ensure that policies are in place that support research review processes that are independent and free of coercion or undue influence.

(5) Establish a process to receive and act on complaints and allegations regarding the HSPP.

(6) Oversee the Central DOE IRBs and formally appoint all members of the Central IRBs.

(7) Approve classified research to be conducted at DOE sites/laboratories after IRB approval and prior to initiation.

(8) Review and adjudicate IRB member appeals of IRB approval determinations for classified projects.

(9) Concur on all requests from Departmental Elements for partial or full exemptions from the requirements of this Order, in order for such requests to be considered for approval.

(10) Approve and rescind authorization agreements with other DOE and outside organizations for IRB review.

e. DOE HSP Program Manager.

(1) Reside within DOE-SC and reports to the DOE IO.

(2) Develop procedures for the HSP program in consultation with the NNSA HSP Program Manager, as appropriate.

(3) Prepare and update guidance to be followed for obtaining approval for HSR in consultation with the NNSA HSP Program Manager, as appropriate.

(4) Review and coordinate with DOE site offices and site IRBs regarding plans to correct any noncompliance or to mitigate adverse study events, ensuring they comply with applicable HSP requirements.

(5) Review and approve statements of work for HTM projects submitted by DOE's non-NNSA sites. Ensure compliance with DOE requirements, and, for HTM projects that are SPPs and SIPP projects; coordinate with appropriate Headquarters SPP/SIPP leads prior to approving such statements of work for initiation. Ensure site offices and M&O contractors are aware of decisions concerning proposed HTM work.

(6) Provide advice and guidance on evolving Departmental and national bioethics and regulatory issues regarding human research subject protection and help identify and resolve program/project concerns in consultation with the NNSA HSP Program Manager, as appropriate.

(7) Develop and conduct 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 HSP Program Manager, as appropriate.

(8) Conduct collaborative quality assurance (QA) consultations at least every 3 years for DOE sites. QA consultations will be designed to provide recommendations for continuous improvement in contractor processes for human subjects' protection.

(9) Serve as the Chair of the DOE Human Subjects Working Group and as the official DOE representative to groups with bioethics and HSP interests. The NNSA HSP rogram Manager shall be invited to attend all such meetings and, as appropriate, to co-chair them.

(10) Make recommendations to the Secretary, after concurrence from, and through the IO, regarding requests for exemptions from any requirements of this Order and satisfies the advance-notice and publication requirements of 10 CFR 745.101(i) prior to the granting of any exemption (in consultation with the NNSA HSP Program Manager, as appropriate).

(11) Concur on HSP provisions in interagency agreements, in consultation with the NNSA HSP Program Manager, as appropriate.

(12) Maintain the HSRD.

(13) Serve as Co-Chair of the Central DOE IRB-C.

f. NNSA HSP Program Manager.

(1) Report functionally to the DOE IO.

(2) When an NNSA element or project is involved, the responsibilities of the NNSA HSP Program Manager are identical to those of the DOE HSP Program Manager.

(3) Ensure compliance with the DOE/NNSA requirements.

(4) Work with the DOE HSP Program Manager, as outlined in Section 5.e.

(5) Serve as Co-Chair of the Central DOE IRB-C.

g. DOE Office of Intelligence and Counterintelligence.

(1) Review and approve, prior to initiation, statements of work for HSR and HTM projects received from members of the intelligence community.

(2) Collaborate with the DOE IO and HSP in overseeing the Central DOE IRB-Classified and provide the Vice Chair and Administrator for this IRB.

h. Secretarial Officers or their Designees.

(1) Ensure that all proposals for research, studies, tests, surveys, surveillance, or other data collection are reviewed to identify the involvement of humans through interaction, intervention, or use of their data or specimens.

(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 HSPP for resolution.

(3) Notify the contracting officer when proposed agreements include research involving humans through interaction, intervention, or use of their data or specimens to ensure the CRD requirements are applied to all affected agreements, incorporating them via the DEAR, Laws, Regulations, and DOE Directives, clause or other appropriate means.

(4) Ensure their staff and field elements comply with the requirements of this Order, and relevant personnel actively participate in human research subjects' protection training and educational programs.

(5) Support, as needed, the DOE HSPP-led QA consultations. QA consultations will be designed to provide recommendations for continuous improvement in contractor processes for HSP.

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

(7) 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, including HSRD reporting.

(8) Ensure that the DOE HSPP concurs in the negotiation of interagency agreements that involve research involving humans through interaction, intervention, or use of their data or specimens.

(9) Appoint a point of contact for interacting with the DOE HSPP on program-related and/or Department-wide issues.

i. Contracting Officer. Once notified that this Order is applicable, incorporate the CRD (Attachment 1) into affected contracts.

j. DOE Field/Site Offices.

(1) Ensure contractor solicitations, contracts, and other agreements for the conduct of research involving humans through interaction, intervention, or use of their data or specimens require compliance with the requirements set forth in the CRD associated with this Order (Attachment 1), 10 CFR 745, and 45 CFR 46.

(2) Ensure that contractors establish and maintain a process for compliance with the requirements set forth in the CRD associated with this Order (Attachment 1), 10 CFR 745, and 45 CFR 46.

(3) Attend the DOE HSPP-led QA consultations, as appropriate.

6. INVOKED TECHNICAL STANDARDS. This Order does not invoke DOE technical standards. Compliance obligations derive from applicable statutes, regulations, and DOE directives cited in this Order.

7. REFERENCES.

a. 10 CFR 745, *Protection of Human Subjects*, which sets the federal requirements for DOE for the protection of human subjects involved in research activities, in alignment with Part A of 45 CFR 46.

b. 45 CFR 46, *U.S. Federal Policy for the Protection of Human Subjects*, known as The Common Rule, Part A of this Department of Health and Human Services regulation aligns with the DOE version 10 CFR 745. References to this regulation within this Order are intended to refer to all subparts, A through E, as applicable to DOE-supported and -conducted HSR, when appropriate.

c. Presidential Memorandum, Strengthened Protections for Human Subjects of Classified Research, dated March 27, 1997, and published in the Federal Register (FR) on May 13, 1997 (62 FR 26369).

d. P.L. 93-348, *The National Research Act of 1974.* This legislation created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which created the foundational ethical framework—*The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. U.S. Department of Health and Human Services. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html

e. 21 CFR 50, *Protection of Human Subjects*, and 56, *Institutional Review Boards;* Part 312: *Investigational New Drug Application* for drugs/biologics; Part 812: *Investigational Device Exemption*; Part 54: *Financial Disclosure by Clinical Investigators*; and Part 11: *Electronic Records; Signatures*.

f. DOE O 443.1C, Chg.1 (LtdChg), *Protection of Human Research Subjects*, November 26, 2019.

g. DOE O 206.1, *Department of Energy Privacy Program*, current version, which ensures compliance with privacy requirements; establishes a Departmental training and awareness program for all DOE federal and contractor employees to ensure personnel are cognizant of their responsibilities for safeguarding PII and complying with the Privacy Act; and provides Departmental oversight to ensure compliance.

h. P.L. 106-65, *National Defense Authorization Act for Fiscal Year 2000*, Title 32, *The National Nuclear Security Administration Act*, 50 U.S.C. 2401 *et seq*.

i. *DOE Policy Memorandum on Research Involving Intentional Modification of the Human Environment*, dated April 25, 2013.

j. *21st Century Cures Act*, (Public Law 114-255) amending the Public Health Service Act (PHS Act), section 301(d) (42 U.S.C. 241(d)) and implementing guidance, which mandates the issuance of a Certificate of Confidentiality for investigators engaged in federally funded research involving certain sensitive, identifiable information about research subjects.

8. DEFINITIONS. See Attachment 2.

9. CONTACT. Questions regarding this Order should be addressed to the DOE HSP Program, HSP Program, SC, BER, telephone (301) 903-3213; or the NNSA HSP Program Manager, as appropriate. Information about the DOE HSPP may be found at https://science.osti.gov/ber/human-subjects.

BY ORDER OF THE SECRETARY OF ENERGY:

JAMES P. DANLY
Deputy Secretary

ATTACHMENT 1
CONTRACTOR REQUIREMENTS DOCUMENT
DOE O 443.1D, *PROTECTION OF HUMAN RESEARCH SUBJECTS*

Regardless of the performer of the work, the contractor is responsible for compliance with the requirements of this Contractor Requirements Document (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:

1. Ensure that human subjects research (HSR),[6] regardless of the source of funding, is conducted in accordance with the principles outlined in the Belmont Report and all applicable federal,[7] DOE-specific, sponsor-specific, and other requirements, including 10 Code of Federal Regulations (CFR) 745, 45 CFR 46, and this CRD.

    a. Maintain a valid Federalwide Assurance (FWA) with the Office of Human Research Protections (OHRP), as described in 10 CFR 745.103.

    b. Ensure that HSR is only initiated after review and approval by an Institutional Review Board (IRB)[8]; or in the case of HSR meeting the categories of exemption at 10 CFR 745.104, has received a determination from an IRB, HSP office, or their designee.

    c. Non-DOE-supported researchers who will conduct HSR at/using DOE/NNSA user facility capabilities must provide documentation of IRB or ethics board approval or exemption determination from their home institution. This HSR is not otherwise required to comply with the provisions of this Order, unless the DOE/NNSA site hosting the facility determines that such compliance is necessary.

2. For DOE-supported or -conducted research that involves humans through interaction, intervention, or use of their data or specimens, but may not constitute HSR per 10 CFR 745.102(e) and (l), the following requirements still apply.

    a. Institutions must adopt a process under which an IRB, HSP office or their designee determines whether proposed research constitutes HSR for the purposes of this Order and the applicability of 10 CFR 745 and 45 CFR 46.

[6] As defined at 10 CFR 745.102(e) and (l), respectively.
[7] Including applicable parts of 21 CFR, Chapter 1, when activities are regulated by the FDA.
[8] As defined in Attachment 2 of this Order.

b. Determinations of whether a project constitutes HSR is required when research involves:

(1) The use of information or specimens for which the identity of the subject is or may readily be ascertained by the investigator or is linked or linkable to the information or specimens.

(2) The study of humans in a systematically modified environment, defined as modification of the human environment in this Order.

(3) Human Terrain Mapping (HTM) activities. Regardless of HSR determination, the following requirements apply to all HTM activities.

(a) At all DOE sites, HTM must be limited to only activities involving the analysis and modeling of de-identified data.

(b) Prior to initiation, statements of work for HTM projects must be submitted to the HSPP for DOE Headquarters review and approval. If the project is to be conducted by or for the intelligence community, such as through strategic partnership projects (SPPs) or SIPP, DOE-IN must also review and approve it prior to initiation.

3. DOE Site IRBs. DOE contractors with internal IRBs registered with OHRP must apply the following requirements, in addition to requiring compliance with this Order during IRB review of protocols.

a. An unaffiliated member must be among the voting IRB members present in order for a DOE Site IRB to conduct business requiring full board review.

b. Ensure HSR that includes engagement of three or more DOE sites as study team members is reviewed by the Central DOE IRB.

c. Researchers who submit studies to the DOE site IRBs and members of these IRBs must complete initial and periodic refresher training in human subjects protection (HSP).

d. IRB records must be maintained and managed in accordance with applicable NARA-approved records schedules.

4. Considerations for HSR.

a. DOE-affiliated personnel as subjects. Targeted inclusion of DOE-affiliated personnel (defined in this Order to include contractor personnel) as participants or the use of their data or specimens, in HSR requires additional consideration to protect potentially vulnerable subjects. Prior to initiation of HSR targeting DOE-affiliated personnel, researchers must obtain:

(1) Written approval from the DOE site being targeted for inclusion, or

(2) Review and approval by the Central DOE IRB when DOE federal employees or more than 1 DOE site are targeted for inclusion, unless an exemption is provided in writing by the DOE HSPP.

b. Personally Identifiable Information (PII). HSR that includes the collection and/or use of PII must adhere to all applicable requirements of DOE Order 206.1A, *DOE Privacy Program,* or current version. This includes safeguarding PII and reporting suspected or confirmed breaches, which are considered Unanticipated Problems, as defined in this Order.

c. International HSR. Contractor conducted and supported HSR, regardless of the location of the activity or participant, domestic or abroad, must adhere to the requirements of this CRD. This policy, however, does not preempt any foreign laws or regulations[9] that may otherwise be applicable, as addressed in 10 CFR § 745.101(g). Where differences in applicable standards exist, the requirements that are most protective of human subjects should be applied.

d. Classified HSR. Ensure that classified and unclassified intelligence and intelligence-related HSR, regardless of funding source (including studies funded through the Strategic Intelligence Partnership Program (SIPP), DOE Office of Intelligence and Counterintelligence (DOE-IN) or other DOE program offices using classified datasets), is reviewed and approved by the Central DOE IRB-Classified.

(1) In addition to IRB approval, HSR that is classified, in whole or in part, must not be initiated without subsequent approval by the DOE IO. The DOE IO, in consultation with the HSPP, will determine whether to approve the project or brief the Secretary about the project prior to their decision.

(2) Informed consent may only be waived for classified HSR if the project meets one or more of the categories of exemption at 10 CFR § 745.104. However, full IRB review will still be required, as categorical exemption from the requirements of 10 CFR 745 and 45 CFR 46 is prohibited for classified HSR.

(3) The use of the expedited review process is prohibited. The fact that research meets a particular expedited category may be noted, however a full IRB review will be required.

(4) The identity of the sponsoring federal agency must be disclosed to subjects, unless the sponsor requests it not be done because it could compromise intelligence sources or methods. Additionally, the research must be no more than minimal risk, and the IRB must determine that not disclosing the identity will not adversely affect the subjects.

[9] In particular, state and international privacy law should be considered.

(5) The informed consent document will state that the project is classified, what that means for the purposes of that project, and the part of the research to which it applies. The IRB must determine whether the potential human subjects need access to classified information to make a valid informed consent decision.

(6) When reviewing classified HSR, the unaffiliated member of a DOE or DOE site IRB must be a non-governmental member (not currently a federal employee or a DOE site contractor employee) with appropriate security clearance.

(7) Any IRB member has the right to appeal the IRB's decision to approve a project to the DOE IO, and if not resolved to the IRB member's satisfaction, may advance to the Secretary of Energy. If still dissatisfied, the IRB member can appeal that approval decision to the Director of the Office of Science and Technology Policy (OSTP), or that Director's designee, or the Director of National Intelligence (ODNI), or that Director's designee. The Director of OSTP, or that Director's designee, or the ODNI, or that Director's designee, will review and approve or disapprove the research, or will convene or designate an IRB that is, to the extent possible, made up of unaffiliated members with the appropriate qualifications and clearance to approve or disapprove the research.

(8) All records related to IRB review/approval of classified HSR, as well as key researcher records must be maintained permanently. During and following the completion of classified research, copies of all signed classified consent forms must be stored in a separate but secure central location (e.g., Security Policy Officer or IRB office), other than the researchers' office, and participants of such research must be notified during the consenting process regarding how to access a copy of their individual signed classified consent forms should they want to in the future.

5. Solicitations and Agreements.

a. Ensure that contractor-issued solicitations or proposals for the conduct of research involving humans through interaction, intervention, or use of their data or specimens includes the requirements of this CRD.

b. Ensure that contracts, financial assistance agreements, and all other agreements issued for the conduct of research involving humans through interaction, intervention, or use of their data or specimens include the requirements of this CRD.

6. Required Reporting.

   a. Prompt notification[10] to the DOE HSPP is required when any of the following occur during performance of contractor conducted or supported HSR, including projects meeting the categories of exemption at 10 CFR 745.104. Contractors should send preliminary notification as soon as reasonably possible.

      (1) Unanticipated Problems[11] involving risks to subjects or others.

      (2) Serious or continuing noncompliance with this Order, 10 CFR 745, 45 CFR 46, or the requirements or determinations of the IRB.

      (3) Suspension or termination of IRB approval.

   b. Human Subjects Research Database (HSRD) Reporting. All contractor conducted and supported HSR, including those projects determined to meet a category of exemption at 10 CFR 745.104, and HSR that targets DOE-affiliated personnel, must be reported to the HSRD as follows.

      (1) Project-specific information, as indicated by the HSPP, must be provided after initial IRB approval or determination of exemption has been obtained.

      (2) Updated project-specific information must be provided every 3 years, or when substantive changes occur, such as any change impacting HSRD reporting categories, study objectives, or upon study completion.

7. Participate in DOE HSPP-led, quality assurance (QA) consultations at least once every 3 years. Collaborative QA consultations will be designed to provide recommendations for continuous improvement in contractor processes for HSP.

8. Requests for exemptions and equivalencies to the requirements of this Order must be submitted to the DOE HSPP.

[10] Defined in Attachment 2 of this Order.
[11] Defined in this Order to include adverse events and data breaches.

ATTACHMENT 2
DEFINITIONS

Key definitions consistent with 45 Code of Federal Regulations (CFR) Part 46 and 10 CFR Part 745.

1. Adverse event. Any unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (Office of Human Research Protections [OHRP], Unanticipated Problems Involving Risk and Adverse Events Guidance, 2007). Adverse events that meet the definition of an Unanticipated Problem involving risk to subjects or others require prompt reporting. The greater the severity of the event, the sooner notification should be provided, including:

    a. Serious Adverse Event (OHRP, Unanticipated Problems Involving Risk Adverse Events Guidance, 2007). Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

        (1) Results in death;

        (2) Is life-threatening;

        (3) Requires inpatient hospitalization or prolongation of existing hospitalization;

        (4) Results in a persistent or significant disability/incapacity;

        (5) Results in a congenital anomaly/birth defect; or

        (6) Is based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

    b. Significant Adverse Event. An adverse event that is unexpected and substantially impacts the subjects.

2. Classified Human Subjects Research. Research involving human subjects that is classified, in whole or in part, in accordance with the federal sponsor and/or DOE criteria.

3. DOE-Affiliated Personnel. Refers to any current or former DOE/NNSA federal or DOE/NNSA contractor (i.e., DOE site) employees.

4. DOE Human Subjects Protection Program (HSPP). The functional program responsible for the requirements of this Order at the DOE level. Managed collaboratively between the DOE Human Subjects Protection (HSP) Program Manager and the NNSA HSP Program Manager, all required communications should be sent to both individuals whenever possible.

5. DOE Site Institutional Review Boards (IRBs). Internal IRBs registered with OHRP for review of research according to 10 CFR 745. DOE Site IRBs must apply the requirements of this Order during review, regardless of funding source.

6. Engagement. When an institution is *engaged* in non-exempt human subjects research (HSR) that is conducted or supported by DOE, it must satisfy Common Rule requirements related to holding an assurance of compliance and certifying IRB review and approval. In general, an institution is considered engaged in a particular non-exempt HSR project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research. (OHRP 2008 Guidance on Engagement of Institutions in Human Subjects Research).

7. Federalwide Assurance (FWA). An assurance of compliance with the U.S. Code of Federal Regulations for the protection of human subjects in research. It is approved by the OHRP for all human subjects research conducted or supported by the U.S. Department of Health and Human Services, as well as for federal-wide use, which means that other U.S. federal departments and agencies that have adopted the *U.S. Federal Policy for the Protection of Human Subjects* (also known as the Common Rule) may rely upon the FWA for the research they conduct or support. The DOE accepts the FWA for compliance with 10 CFR 745.103. (OHRP website on FWAs).

8. Generalizable Knowledge. When considering the regulatory definition for research (10 CFR 745.102[l]), the DOE defines "generalizable knowledge" as information that expands the knowledge base of a scientific discipline or other scholarly field of study. An example would be research findings that are intended to be applied to populations or situations beyond those studied.

9. Human Subjects Protection (HSP) Office. An institutional role or group with HSP training and sufficient knowledge to serve as a subject matter expert in HSR related questions. Usually, this office is associated with an IRB.

10. Human Subjects Research. As defined at 10 CFR 745.102(e) and (l).

11. Human Subjects Research Database. A comprehensive database of all HSR that is DOE-supported or -conducted or enrolls DOE-affiliated personnel. Reporting of projects to this database is required for all HSR, even when it meets the categories of exemption at 10 CFR 745.104, and may be completed by the researchers conducting the project, the HSP office, or the IRB reviewing the project, or any other institutional representative.

12. Human Terrain Mapping (HTM). Research and data gathering activities primarily conducted for military or intelligence purposes to understand the "human terrain"—the social, ethnographic, cultural, and political elements of the people among whom the U.S. Armed Forces are operating and/or in countries prone to political instability. This work includes observations, questionnaires, and interviews of groups of individuals, as well as modeling and analysis of collected data, and may become the basis for U.S. military actions in such locations. In addition to HTM, such activities are often referred to as human social culture behavior studies. HTM activities must have an HSR determination.

13. 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.

14. Institutional Review Board. A committee or board established by an institution that performs initial and continuing reviews of HSR. Review of DOE-supported or conducted HSR requires IRBs to be registered with the OHRP in accordance with 45 CFR 46, Part E, and designated on an approved FWA.

15. Modification of the Human Environment. A category of research commonly conducted to evaluate the performance of new technologies in real world environments. Defined for the purposes of this Order as research:

    a. In which people have their environment intentionally changed or manipulated for the purposes of the research, with or without their knowledge; and/or

    b. That cannot be validly conducted without people present (other than those conducting the research), regardless of whether identifiable private information is collected about them.

16. Personally identifiable information (PII). Review DOE O 206.1A, or current version, regarding definitions of PII and accompanying DOE requirements.

17. Prompt notification. The regulations do not define *prompt*. The appropriate time frame for satisfying the prompt reporting requirement will vary depending on the specific nature of the Unanticipated Problem, the nature of the research associated with the problem, and the entity to which reports are to be submitted. Determining the appropriate time frame for reporting a particular Unanticipated Problem requires careful judgment by persons knowledgeable about human subject protections. The primary consideration in making these judgments is the need to take timely action to prevent avoidable harm to other subjects.

    The requirement for prompt reporting is met by submitting a preliminary notification to the DOE HSPP, preferably within 1 week, followed by a report of corrective actions taken, at the HSPP's discretion.

18. Strategic Intelligence Partnership Program (SIPP). SIPP, formerly the Intelligence Work for Others program, is the mechanism by which DOE provides highly specialized scientific and technical services and products to non-DOE intelligence community (IC) and other agencies for intelligence and intelligence-related activities carried out under unique IC authorities held by DOE Office of Intelligence and Counterintelligence and sponsoring IC agencies.

19. Strategic Partnership Projects (SPPs). SPP, formerly the Work for Others program, is the mechanism by which non-DOE entities fund DOE/NNSA and/or their contractors or use DOE/NNSA facilities for work that is not directly funded by DOE/NNSA appropriations.

20. Unaffiliated IRB member. For review of unclassified protocols, an unaffiliated IRB member must not have a direct affiliation (e.g., current or former employee, contractor, student in a fellowship, volunteer at the institution, or business related to the IRB, and must not have an immediate family member who is affiliated with the institution). For review of classified protocols, one must be a non-governmental member (not currently a federal employee or a DOE site contractor employee) with the appropriate security clearance.

21. Unanticipated Problem. An occurrence (including adverse events and data breaches) associated with HSR meeting all three of the following criteria is required to be reported promptly to the DOE HSPP:

    a. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.

    b. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).

    c. Likely to place subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.