

Standard Operating Procedure

Central DOE Institutional
Review Board-Classified
(CDOEIRB-C)

July 2015



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Revision Log

Standard Operating Procedure

Central DOE Institutional Review Board – Classified

Revision No.	Date	Changes Description	Page Modified	Signature of Approval Official
Original	June 15, 2012	Issued Procedure	None	All Management and Administrative Team Members and Institutional Official
1	October 2013	Condensed chapter 1; refined roles and responsibilities, including making the Chair a voting member, eliminating the associate IRB manager position, and adding a security officer to advise the administrative and management teams on security and classification issues; clarified policies and procedures for IRB review and classification review of IRB-generated documents; and clarified and expanded scope of work (to address projects involving manipulation of the human environment and to include HTM and intelligence-related HSR from DOE sites that do not have internal IRBs).	Multiple	All Management and Administrative Team Members and Institutional Official
2	September 2014	Updated Attachments II and IV, added Attachment V, clarified the section on additional approval requirements, Chapter I, made several changes to roles and		Management Team and Chair

		responsibilities (Chapter 3), and updated references and definitions in Chapters 11 and 12.	
3	October 2014	Modified Chapter 1 to clarify requirements for DoD-funded projects that are conducted by other Common Rule agencies	Management Team and Chair
4	July 2015	Revised to incorporate changes agreed to by DOE, NNSA, and IN for the second term of the CDOEIRB-C.	
		Modified Chapter 1 to clarify requirements for DoD-funded projects; Modified Chapter 2 to include specific requirements of several sponsors; Modified Chapter 3 to clarify roles and responsibilities, including eliminating the “Management Team” and aligning roles with those agreed to by IN and the IO; Modified Chapter 4 to clarify responsibilities, requirements for nomination/selection of members; Modified Chapter 5 to clarify language regarding waivers of informed consent and to provide additional detail regarding process; Modified Chapter 6 to provide additional detail regarding process . Also modified Attachment II, deleted Attachment IV, replacing it with (previous) Attachment V, and added a Attachment V, VI, and VII	

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Central DOE Institutional Review Board - Classified

After consultation with the DOE Institutional Official, this Standard Operating Procedure was reviewed and approved by:



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Acronyms

CDOEIRB-C	Central Department of Energy (DOE) Institutional Review Board (IRB) - Classified
CITI	Collaborative Institutional Training Initiative
CFR	Code of Federal Regulations
DHHS	U.S. Department of Health and Human Services
DOE	U.S. Department of Energy
FDA	U.S. Food and Drug Administration
FWA	Federalwide Assurance
FWP	Former Worker Medical Screening Program
HSPP	Human Subjects Protection Program
HSR	Human Subjects Research
HTM	Human Terrain Mapping
IAA	IRB Authorization agreements
IDE	Investigational Device Exemption (FDA)
IN	DOE Office of Intelligence and Counterintelligence
IND	Investigational New Drug (FDA)
IO	Institutional Official
IRB	Institutional Review Board
NNSA	National Nuclear Security Administration (quasi-independent agency within DOE)
OHRP	DHHS Office for Human Research Protections
PHI	Protected Health Information
PII	Personally Identifiable Information
POC	Point of Contact

SOP Standard Operating Procedure

SC DOE Office of Science

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CHAPTER 1: PURPOSE, BACKGROUND, AND SCOPE

Purpose

The purpose of this manual is to document the Standard Operating Procedure (SOP) [10 Code of Federal Regulations (CFR) Part 745.103(b) (4) & (5) and [DOE Order 443.1B](#)] of the Central Department of Energy (DOE) Institutional Review Board (IRB)-Classified (CDOEIRB-C), or the Board. The functions of the CDOEIRB-C are to assure that the risks to human participants involved in research under its purview, are minimized and reasonable in relation to the anticipated benefits and to protect the rights and welfare of study participants in accordance with applicable Federal regulations, State Laws, DOE Directives and existing ethical principles. To carry out its duties, The Board operates in accordance with this SOP, but with independence and autonomy in its review and deliberative process.

History, Background and Scope

DOE established the CDOEIRB-C in 2012. The scope of the CDOEIRB-C is to review all intelligence work for others human subjects research and/or human terrain mapping (HTM)* projects falling under the Strategic Intelligence Partnership Program (SIPP) that are sensitive in nature or classified, in whole or in part, and are conducted at a DOE facility/site without an internal IRB, or without an internal IRB capable of reviewing such projects in their entirety due to classification or other reasons. All classified or sensitive SIPP projects that involve more than one DOE Laboratory also fall under the purview of the Central DOE IRB-C. Typically, these projects are funded by outside agencies and conducted by DOE sites/laboratories or by DOE employees/contractors at other institutions. Additionally, at the request of DOE site/laboratory IRBs and/or the Human Subjects Protection Program (HSPP) Managers, the CDOEIRB-C will review non-intelligence classified projects if the sites are unable to review them internally. Members of the CDOEIRB-C have the necessary security clearances needed to review these projects.

As background, federal human subjects protection regulations do not distinguish between classified and unclassified research in the requirements they impose, other than to disallow use of expedited review for classified research. DOE follows the cumulative best practices that have evolved from hands-on experience with classified research by DOE site/laboratory IRBs, as well as the 1997 “Clinton Memorandum on Strengthened Protections for Human Subjects of Classified Research,” and sponsor-specific requirements.

**[DOE Order 443.1B, Protection of Human Research Subjects](#), Section 4a(2), dated March 17, 2011, outlines DOE requirements for HTM activities. DOE limits engagement of its Laboratories in HTM projects to: 1) development of models and software for use by the Department of Defense (DoD) and other Federal agencies in their analyses of collected HTM data; and 2) analysis of de-identified as defined in the definitions section of this Standard Operating Procedure (SOP) or*

publicly available data. It is DOE's policy that, prior to initiation, such projects be approved by DOE Headquarters, the DOE or NNSA human subjects protection (HSP) program manager (see Chapter 3), and if intelligence-related, also IN. DOE Headquarters will engage the CDOEIRB-C and, potentially, the DOE laboratory principal investigator (PI), in confirming that the intention of the PI is to work only with de-identified or publicly available data. Once the project is initiated, the recognized DOE IRB (and in the case of DOE laboratories that do not have their own site IRB, the CDOEIRB-C) is the only entity authorized to determine whether the HTM data received by the PI after project initiation meets the DOE criteria for de-identification. Using the DOE-provided HTM Data Review Process/Standard Operating Procedure (see IRB manager for a copy), the CDOEIRB-C is responsible for working with certain DOE laboratory PIs to: 1) discuss the datasets received from the sponsor and/or any other data to be used to ensure they are sufficiently de-identified for the PI to begin work; and 2) complete and sign a data security agreement with the PI using the DOE-provided template. DOE also expects that the CDOEIRB-C will periodically (not less than once a year) follow up with the PI to check on progress and scope of the work being conducted. Any modifications in scope would require both Headquarters and CDOEIRB-C approval.

Note: In general, classified human subjects research is not to be conducted on the vulnerable populations identified in Subparts B, C, and D of 45 CFR Part 46. Any deviation from this policy requires approval by the DOE Institutional Official (IO)— see chapter 3.

Additional Approval Requirements

Classification Review:

Before any information regarding classified projects is released, it must be reviewed for classification. Unless otherwise marked, all information will be treated and marked as official use only (OUO). Sponsors should also provide copies of any classification guides applicable to their project(s).

DOE-Specific Requirements:

Following review/approval by the CDOEIRB-C and prior to initiation, the DOE IO, who has been delegated responsibility for oversight of the implementation of the DOE Human Subjects Protection Program and the Central DOE IRBs by the Secretary, must approve projects that are classified in whole or in part. For classified projects above minimal risk, the DOE IO will determine if the Secretary should approve, be briefed, or be notified of the project (see Attachment IV).

DoD-Specific Requirements

All Department of Defense (DoD) funded work, including DoD intelligence-related human subjects research, must comply with DoD Instruction [3216.2, Protection of Human Subjects and Adherence to Ethical Standards in DoD-supported Research](#). Typically, DoD requires Secretary of DoD approval for classified research. However, in certain instances (see Attachment V), DOE will perform the second tier review on behalf of DoD.

Other Agencies' Requirements

The DOE and NNSA human subjects protection (HSP) program managers will be responsible for communicating the requirements of each sponsor to the CDOEIRB-C.

Potential Future Expansion of the Scope

Several emerging, and/or currently unidentified issues or topics may present challenges that are serious enough to warrant review and oversight by the CDOEIRB-C. The IN Manager and the HSP Program Managers will make a collective determination on a case-by-case basis regarding those issues that need to be addressed by the CDOEIRB-C.

For purposes of the CDOEIRB-C, when questions or uncertainties arise regarding the applicability of human subjects protection regulations, the HSPP Managers will provide guidance in consultation with the DOE IO, as appropriate.

CHAPTER 2: OVERVIEW

Numerous Federal statutes set forth the requirements and expectations for IRB performance. The root of these requirements is the fundamental desire that every human research subject be treated with respect, dignity, and an assurance that risk will be held to the lowest achievable level, consistent with the goals of the research. The principles that underlie the protection of human subjects today are found in three main documents:

[The Nuremberg Code](#)¹

[The Belmont Report](#)²

[The Declaration of Helsinki](#)⁴,

Basic Ethical Principles

The CDOEIRB-C is guided by the ethical principles set forth in these documents, including the following three principles outlined in the Belmont Report:

Respect for Persons: requires that potential subjects be given the information they need, in language they understand, to decide whether or not to participate in a study, as well as the time and opportunity necessary to make that decision without any pressure to participate.

It further requires protection of subject privacy, confidentiality of data, and increased protection for vulnerable populations.

Beneficence: requires that researchers (and their institutional organizations) minimize the probable risks and maximize the potential benefit(s) to the subjects and/or society in which they participate.

Justice: requires that the benefits and burdens of research be distributed fairly. Subjects should be recruited on the basis of their relation to the problem under study rather than their easy availability, their compromised position, or their malleability. Investigators should base inclusion/exclusion criteria on those factors that most effectively and soundly address the research problem. For example, subjects should not be denied access to a study simply because they may not speak English.

1 Reprinted from Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181-182. Washington, D.C.: U.S Government Printing Office, 1949

2 The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979

4 Link may not include latest version, as this is a living document that changes regularly.

IRB Role

IRB Review Requirements

All domestic and foreign institutions or sites where research involving human subjects is conducted or funded by DOE or that use information or data on DOE employees are required to perform this research in keeping with applicable Federal regulations (45 CFR Part 46, *Protection of Human Subjects*), and DOE-specific requirements (articulated in 10 CFR Part 745, *Protection of Human Subjects* and DOE Order 443.1B, *Protection of Human Research Subjects*). Subpart A of the federal regulations, 45 CFR Part 46, is replicated word for word in the DOE-specific regulations, 10 CFR Part 745. While 10 CFR Part 745 does not address the additional sub-parts of 45 CFR Part 46 (protection of vulnerable subjects), DOE Order 443.1B requires compliance with these additional sub-parts.

The Federal oversight office for human research, the DHHS Office for Human Research Protections (OHRP), requires prospective and continuing review and approval of human subjects' research activities by a committee, usually called an IRB. The primary mandate of IRBs is to protect the rights and welfare of humans who are the subjects of research. Regulations require that the membership of the IRB be diverse in order to provide expertise in and sensitivity to a broad range of scientific and ethical considerations.

As mentioned above, DOE requires that all IRBs under its purview comply with [10 CFR Part 745](#) (which is identical to Subpart A of 45 CFR Part 46), and also with [45 CFR Part 46](#), Subparts B, C, D, and E, as well as [DOE Order 443.1B](#). DOE is authorized per 10 CFR Part 745.101(d), to impose additional protections. The CDOEIRB-C is also required to comply with DOE Order 471.6, *Information Security*, and with the 1997 Clinton Memorandum on "*Strengthened Protections for the Human Subjects of Classified Research*."

Criteria for IRB Approval of Research Involving Human Subjects

Federal regulations allow an IRB to approve research only after it has determined that all of the following requirements are satisfied (per 10 CFR Part 745.111):

- (1) Risks to subjects are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk. Whenever appropriate, researchers should employ procedures that are being performed on subjects for diagnostic or treatment purposes.
- (2) Risks to subjects are reasonable, relative to:
 - a. anticipated benefits, if any, to subjects, and
 - b. the importance of the knowledge that may reasonably be expected to result.
- (3) The selection of subjects is fair and equitable, taking into account the purposes of the research and the setting in which it will be conducted. The IRB must be particularly

attentive (including requiring additional safeguards, as needed) to any special problems that may arise when research involves employees or others who might be susceptible to undue influence or coercion. Classified human subjects research funded or conducted by DOE must not involve the vulnerable populations addressed in Sub-parts B, C, and D of 45 CFR Part 46: pregnant women, children, and prisoners. Exceptions to this requirement may be considered by the IRB only if first approved by the DOE IO.

- (4) Informed consent will be sought from each prospective subject, or the subject's legally authorized representative, generally by means of a written consent document. The IRB will carefully review these documents to assure that they contain the required elements of informed consent (see 10 CFR Part 745) and are understandable to a lay person.
- (5) Informed consent will be appropriately documented, in accordance with, and to the extent required by, 10 CFR Part 745.117.
- (6) The research plan makes adequate provisions for ensuring the safety of subjects.
- (7) There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- (8) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects. DOE considers current and former employees to be a vulnerable population (Attachment VII) and the Board must consider whether appropriate safeguards have been provided. These requirements are incorporated in the CDOEIRB-C review standards. For all initial protocol reviews, these standards must be addressed and recorded in the minutes.

CDOEIRB-C PROTOCOL REVIEW STANDARDS

Minimal regulatory requirements for IRB review

Regulatory review requirement	Suggested questions for IRB discussion
1. The proposed research design is scientifically sound and will not unnecessarily expose subjects to risk.	<ol style="list-style-type: none"> (a) Is the hypothesis clear? Is it clearly stated? (b) Is the study design appropriate to test the hypothesis? (c) Will the research contribute to generalizable knowledge and is it worth exposing subjects to risk? (Note: Generalizable, in classified research, should be viewed in terms of its contribution to knowledge within the intelligence community and/or the scientific contribution to the specific field of study.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of knowledge that may reasonably be expected to result.	<ol style="list-style-type: none"> (a) What does the IRB consider the level of risk to be? (b) What does the PI consider the level of risk/discomfort/inconvenience to be? (c) Is there prospect of direct benefit to subjects or to the advance of scientific knowledge?

CDOEIRB-C PROTOCOL REVIEW STANDARDS

Minimal regulatory requirements for IRB review

Regulatory review requirement	Suggested questions for IRB discussion
3. Subject selection is equitable.	(a) Who is to be enrolled? Men? Women? Ethnic minorities? (b) Are these subjects appropriate for the protocol?
4. Informed consent is obtained from research subjects or their legally authorized representative(s).	(a) Does the informed consent document include the eight required elements (see below)? If greater than minimal risk, the sponsor must be disclosed. (b) Is the consent documenting a language they understand and conveyed in a manner they understand?
5. Informed consent will be appropriately documented in accordance with, and to the extent required by, 10 CFR Part 745.116.	(c) Who will obtain informed consent (PI, other) and in what setting? (d) Is the IRB requested to waive or alter any informed consent requirement?*
6. The research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.	(a) What is the nature and scope of foreseeable risks to the subjects? (b) Does the research design minimize risks to subjects? (c) Would use of a research oversight process enhance subject safety?
7. Subject privacy and confidentiality are maximized.	(a) Will personally identifiable research data be protected to the extent possible from access or use? (b) Are any special privacy and confidentiality issues properly addressed? (c) Should a data management plan be required? (d) Should a certificate of confidentiality be requested?
8. If vulnerable populations are involved, additional safeguards have been included.	(a) Are individuals who might be subject to coercion or undue influence involved in the research? (b) DOE also considers current and former employees a vulnerable population (Attachment VII) and thus asks that its reviewers consider whether appropriate safeguards have been provided. For example, it is important that: 1) to the extent possible, employees reporting to the PI not be allowed to participate in the study; 2) any employee who participates in the study be informed that participation is voluntary and there will be no ramifications of pulling out of the study at any time; and 3) the contact information for the DOE/NNSA HSPP managers be provided on informed consent forms, in case study subjects would like to contact an individual who is not engaged in or affected by the study, yet understands the DOE HSPP requirements.
Additional considerations	
1. Ionizing and non-ionizing radiation, as well as other biological insults	(a) Is it medically indicated or for research use only? (b) Is there need for review by a radiation safety committee?

CDOEIRB-C PROTOCOL REVIEW STANDARDS

Minimal regulatory requirements for IRB review

Regulatory review requirement	Suggested questions for IRB discussion
2. Cooperative research	<ul style="list-style-type: none"> (a) Is this domestic/international cooperative research? (b) If so, are FWAs or other assurances required for the sites involved? (c) Is there a Cooperative Research and Development Agreement?
3. FDA-regulated research	<ul style="list-style-type: none"> (a) Is an IND or IDE involved in this protocol? Note the FDA-specific requirements.
Sponsor and DOE-specific Requirements	<p>See also 9 on the next page</p> <p>For projects that are greater than minimal risk, a research monitor is required (See Section 8a, DoD Instruction 3612.02).</p> <p>For classified projects (as determined to be projects for which the following information is classified: 1) information needed for IRB approval and oversight; 2) information needed to inform subjects during the consent process; and 3) information provided by subjects during research), the following is required:</p>
DoD	<ul style="list-style-type: none"> 1) Following DOE IO approval, Secretary of Defense approval, with the exception of projects addressed in Attachment VI of these SOPs: -2) o waivers of informed consent; -3) In the consent document for projects that are greater than minimal risk, of the sponsoring organization; 4) -Statement in the informed consent that research is classified.
DOE Requirements for implementation of the 1997 Presidential Memorandum on Strengthened Protections for Human Subjects of Classified Research	<p>DOE requires that, for all research that is classified, in whole or in part, the following requirements of the Clinton Memorandum be met:</p> <ul style="list-style-type: none"> 1) No waivers of informed consent 2) No expedited reviews of such projects 3) The identity of the sponsoring agency must be disclosed to the subjects, unless providing this information could compromise intelligence sources or methods and the research involves no more than minimal risk. 4) Projects must be reviewed/approved by a voting quorum of five IRB members, which includes an unaffiliated member, who is a non-governmental member (and also not a DOE site/laboratory employee) with the appropriate security clearance.”

Nine Required Elements of Informed Consent

- (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 that 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 that 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/or 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.
- (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.
- (9) For all classified research conducted at DOE sites, informed consent forms must include:
 - a) identification of the sponsoring institution of the research,;
 - b) a statement that the research involving human subjects is classified and an explanation of the impact of the classification. * This 9th element is in addition to those required by Federal Regulation 45 CFR Part 46.

Note: The CDOEIRB-C shall also determine whether potential subjects need access to classified information to make a valid informed consent decision.

Risk/Benefit Assessment

Regulatory definition of minimal risk: the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [10 CFR Part 745.102(i)]. Risks considered to be minimal for most individuals may be considered greater than minimal in a vulnerable population.

The risk categories used by the CDOEIRB-C are:

- The research involves no more than minimal risk to subjects;
- The risk(s) represents a minor increase over minimal risk; or
- The risk(s) represents more than a minor increase over minimal risk.

Benefit: A research benefit is something of health-related, psychosocial, or other value to an individual research subject, or something that will contribute to the acquisition of generalizable knowledge. Money or other compensation for participation in research is not considered a benefit. Benefits will typically fall into one of the following categories:

- No prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition;
- No prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge to further society's understanding of the disorder or condition under study; or
- The research involves the prospect of direct benefit to individual subjects.

CHAPTER 3: AUTHORITIES AND RESPONSIBILITIES

Protecting the subjects of research is a shared responsibility involving institutional officials, research investigators, IRBs and research subjects.

DOE

DOE shall operate and maintain the CDOEIRB-C in accordance with 10 CFR Part 745 and with 45 CFR Part 46, *Protection of Human Subjects*, Sub-parts B, C, D, and E, as well as DOE Order 443.1B and DOE Order 471.6, *Information Security*. Note that for all research falling under the purview of this IRB, research under Sub-parts B, C, and D may only be conducted following approval by the DOE IO. All classified projects under the purview of the CDOEIRB-C require approval of the DOE IO (see Attachments IV and V).

Senior DOE Official for Human Subjects Research (Institutional Official (IO))

The Associate Director of Science for the Office of Biological and Environmental Research is the senior DOE official, or DOE IO, and is responsible for:

- Ensuring the CDOEIRB-C complies with applicable Federal regulations and DOE-specific requirements;
- Ensuring that the OHRP Federal wide Assurance (FWA) and CDOEIRB-C registration are properly maintained and current;
- Issuing appointment letters to Board members;
- Terminating members for cause, with input from the CDOEIRB-C Administrative Team;
- Following CDOEIRB-C approval, approving (on behalf of the Secretary), each project that is classified, in whole or in part.

Office of Intelligence (IN)

IN will be responsible for providing the appropriate security clearances for the CDOEIRB-C members with financial support from SC, as needed. IN will also be responsible for certain resources required to operate the CDOEIRB-C (Administrator, filing space, communications on the high side, etc.). An individual from IN (IN Manager) will be responsible for working with the DOE HSP Program Managers to review recommendations for membership.

Human Subjects Protection (HSP) Program Managers

In addition to their responsibilities specified in DOE Order 443.1B, the [DOE HSP Program Manager](#) (SC-23.2) and the [NNSA HSP Program Manager](#) (NA-50) are responsible for:

- Ensuring this SOP is up-to-date and coordinating its approval with the IN Manager in consultation with the DOE IO.
- Making joint recommendations to the DOE IO in all matters of the HSPP.
- Ensuring the Board Members have access to DOE required training.
- Reviewing/approving corrective action plans to correct any noncompliance or to mitigate adverse study events.
- Annually rotating as IRB Chair; and when the Chair is unable to serve in that role for any reason, temporarily taking on that responsibility on his/her behalf.

CDOEIRB-C Administrative Team

The CDOEIRB-C Administrative Team consists of the CDOEIRB-C Chair, Vice Chair, and CDOEIRB-C Manager, or Administrator. They are responsible for completing initial DOE-required training, CITI, (following appointment) and completing refresher CITI Training every three years. Additionally, they are expected to take initial and continuing training required by their DOE organizations on managing and handling classified information.

Specific additional responsibilities for the Chair, Vice Chair, and IRB Administrator are noted below.

Chair

The Chairperson (Chair) is responsible for providing professional leadership and ensuring that the Board carries out its responsibilities. The Chair votes only in the case of a tie. The Chair will alternate annually on June 15, between the NNSA and DOE Human Subjects Protection Program managers. In the event of a COI or inability to participate at a convened meeting, the other HSPP manager will assume the role of Chair for that meeting. Chair responsibilities include but are not be limited to the following:

- Performing Chair functions at meetings;
- In consultation with the Administrative Team, as appropriate, making and communicating determinations regarding conflict of interest;
- Concurring on any CDOEIRB-C authorization agreements (IAA) with collaborating (institutional or site) IRBs, which are signed for the CDOEIRB-C by the DOE IO

- Making initial determinations regarding adverse events, unanticipated problems, and serious/significant or continuing non-compliance;
- Communicating and collaborating with the DOE IO, PIs, and/or Chairs or members of other IRBs as appropriate (i.e., regarding adverse events, unanticipated problems, and serious/significant or continuing non-compliance);
- Setting the meeting agenda;
- Ensuring the timely review of research protocols; and
- Making a determination (either based on a review by the Administrative Team or by other Board members) as to whether HTM data received by the PI following DOE approval and project initiation meets DOE criteria for de-identification.

Vice Chair

- The CDOEIRB-C Vice Chair is a representative from IN and has the following responsibilities:
- Acting as Chair in the absence of either HSP Program Manager's ability to Chair the convened meeting, either because of COI or inability to participate in the discussions; and
- Assisting with Board activities, as requested by the Chair.

CDOEIRB-C Administrator

- The CDOEIRB-C Administrator is a non-voting member, from IN, and is responsible for the following:
- Serving as primary point of contact (POC) for the CDOEIRB-C for CDOEIRB-C Members, PIs, and other institutional IRBs;
- Verifying that members and PIs have completed all required training;
- Assisting with the determination of who will serve as primary and secondary reviewers;
- Scheduling meetings and related travel of the Board and others as needed;
- Reviewing all submitted materials for completeness and distributing materials to Board members;
- Notifying the DOE/NNSA HSP Program Managers of all research that will involve participation of the DOE and/or contractor workforce as human research subjects, upon receipt of a PI request for CDOEIRB-C review.

- Generating minutes of meetings;
- Generating and providing all correspondence to CDOEIRB-C Members, PIs, and other involved institutions, as appropriate;
- Working with the Chair and other HSP Program Manager to populate the appropriate IT system with all pertinent unclassified project information, with the appropriate designator that the information will not be downloaded to the HSRD, and
- Maintaining all CDOEIRB-C records, including training records.
- In the event that the CDOEIRB-C Administrator position becomes vacant, the HSP Program Managers, in consultation with IN and the DOE IO, will select an interim Administrator until another CDOEIRB-C Administrator is appointed.

Members

- Members' responsibilities are as follows:
- Completing initial DOE-required training, [CITI](#), following appointment;
- Completing refresher CITI training every three years, as required by DOE;
- Completing and documenting to the CDOEIRB –C Administrator all required security training.
- Informing the Chair or member of the Administrative Team if they have a conflict of interest with a proposed or ongoing study;
- Attending scheduled meetings;
- Reviewing all materials distributed by the CDOEIRB-C Administrator prior to scheduled meetings;
- Participating as primary or secondary reviewers when requested by the Chair, Vice Chair, or CDOEIRB-C Administrator;
- When requested by the Chair, serving as a member of the team responsible for evaluating one or more projects (after initial reviews) to assess/verify compliance with the requirements of the SOP and other applicable DOE and Federal requirements.
- Performing other CDOEIRB-C-related activities when requested by the Chair, Vice Chair, or CDOEIRB-C Administrator; and
- Managing all classified protocol information in accordance with DOE Order 471.6, *Information Security*.

Principal Investigators

- Principal Investigators' (PIs') primary responsibilities are to protect the rights and welfare of human research subjects and comply with all applicable provisions of Federal law, any special requirements of the DOE, and any requirements set by the CDOEIRB-C. The PIs must be familiar with the ethical principles of human subjects research and the requirements of Federal regulations, DOE directives, and applicable state laws. PIs must not begin research tasks involving human subjects until IRB approval has been secured. PIs must comply with CDOEIRB-C decisions, directives, conditions of approval, and other responsibilities, including:
 - Submitting required materials to the CDOEIRB-C for review and approval in a timely manner, (preferably at least 4 weeks prior to Board meetings) for which the protocol is scheduled to be discussed;
 - Justifying the need to involve human subjects in research;
 - Ensuring that all risks to subjects associated with the protocol are understood and clearly communicated and that each potential subject clearly understands the nature of the research;
 - Providing a copy of the signed CDOEIRB-C-approved informed consent document to each participant at the time of consent unless the CDOEIRB-C has specifically waived this requirement;
 - Ensuring that all signed consent documents are retained in accordance with the terms of DOE's contract, grant, or cooperative agreement or DOE's applicable records retention schedules, regardless of the funding source;
 - Ensuring that subject privacy and data confidentiality are protected in accordance with applicable requirements and providing evidence of compliance with DOE requirements for the protection of PII;
 - Ensuring that research is conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA) requirements, as applicable;
 - Promptly reporting any proposed changes in previously approved research to the CDOEIRB-C, and not initiating changes without approval by the CDOEIRB-C;
 - Reporting progress of approved research to the CDOEIRB-C as often as, and in the manner prescribed by, the CDOEIRB-C, but not less than annually;
 - Promptly reporting to the CDOEIRB-C any adverse events or unanticipated problems involving risks to subjects or others, in accordance with DOE Order 443.1B;
 - Notifying the CDOEIRB-C when the project is complete or needs to be inactivated;

- Notifying the Food and Drug Administration (FDA) and the Board whenever it is anticipated that an investigational new drug (IND) or investigational device exemption (IDE) will be required;
- Providing evidence of professional credentials (CV or resume`), and initial and refresher training in human subjects protection (through CITI or comparable training provider) for all members of the research team who interact with subjects and/or have access to PII prior to commencement of research activities; and
- Prior to initiation of HTM projects, ensuring: 1) approval by DOE Headquarters [[see DOE Order 443.1B, Section 4a\(2\)](#)]; and 2) that the CDOEIRB-C has been provided with written verification that only de-identified data, as defined in this SOP, will be used. After project initiation and before beginning work, following the DOE-approved procedures to ensure appropriate CDOEIRB-C review and approval of any datasets to be used.

CHAPTER 4: CDOEIRB-C STRUCTURE

Membership

The CDOEIRB-C will comply with the membership requirements of 10 CFR Part 745.107. The CDOEIRB-C will be composed of federal employees only, with the exception of the unaffiliated members. The Board must have at least five members with various backgrounds to promote complete and adequate review of human subject research activities. The Board membership will be sufficiently qualified through the experience, expertise, and diversity of its members, including consideration of race, gender, 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.

The CDOEIRB-C membership will be assessed annually at the beginning of each fiscal year to ensure that the Board is responsive to the areas of research under its purview and that the requirements of 10 CFR Part 745.107 are fully satisfied. Membership of the CDOEIRB-C will include the following:

- Equitable and reasonable gender representation;
- At least one member whose primary concern is with scientific matters;
- At least one member whose primary concern is with nonscientific matters; and
- At least one unaffiliated member. For purposes of the CDOEIRB-C, an unaffiliated member is an individual who is not currently a Federal or DOE Laboratory/Site employee.

Additional members may include the following:

- One expert in the protection of personally identifiable information and information security.
- Technical experts with expertise in the types of research reviewed by the Board.

The CDOEIRB-C may also invite individuals with competence in special areas to assist in the review of studies that require their specific area of expertise. These individuals will leave the room before final discussions and will not have a vote.

Members will not participate in initial or continuing review of any project in which they have a conflict of interest.

It is DOE's policy to pay for non-federal members' honoraria, and appropriate travel expenses for all members, in accordance with DOE guidelines. DOE will also cover the costs of and

travel required for CDOEIRB-C purposes for federal members of the CDOEIRB-C, and for liability insurance for the unaffiliated members. No other expenses will be paid unless a request with the justification is submitted to and approved by the DOE and/or NNSA HSP manager(s).

Selection and Appointment of Members, Vice-Chair, and Chair

Recommendations for Membership: Recommendations for CDOEIRB-C membership, excluding the positions of Chair and Vice Chair, may be made to the DOE IO through the HSP Program Managers, by any member of the Board and by DOE/NNSA/IN officials associated with the CDOEIRB-C. Potential members will be asked to provide a resume to the CDOEIRB-C Administrator, who will share the information with the HSP Program Managers and the IN Manager. They will make recommendations to the DOE IO, who will determine the final board composition/membership. The Chair and Vice Chair positions are designated as described in these SOPs.

Appointment: Board members will receive a letter of invitation from the DOE IO.

Chair and Vice Chair Terms: The Chair will alternate annually on July 16th, between the NNSA and DOE HSP Program Managers. In the event of a COI or inability to participate at a convened meeting, the other HSP program manager will assume the role of Chair for that meeting. The Vice-Chair will serve a three-year term and will act as Chair in the absence of either HSP Program Manager's inability to Chair the convened meeting, because of COI or inability to participate in the discussions

Board Members' Terms: Board Members will serve three-year terms. Terms will end on July 15, 2018 and every three years thereafter.

Additional Terms: Additional terms may be served by any member of the Board, if desired, and if re-appointed by the DOE IO through a letter based on recommendations by the Chair, Vice Chair, and the HSP Program Managers.

Liability Insurance for Members: DOE, through the Oak Ridge Institute for Science and Education (ORISE), will provide liability insurance for all unaffiliated members. Members who are DOE Federal employees may want to buy their own coverage. .

Resignation/Termination of Members: Members may resign from the CDOEIRB-C at any time, but fulfilling existing terms is encouraged. In the event of a member's resignation before fulfilling the existing term, three months' notification in writing is requested, along with the reason for discontinuing membership.

Termination of a member by the DOE IO from the CDOEIRB-C prior to expiration of his or her term requires documented "just cause" to show that continuation or renewal of a member's term would be detrimental to the CDOEIRB-C. Just cause for removal may include, but is not limited to, unexcused absences for more than 50 percent of the meetings in a year, loss of clearance, misconduct, unresolved conflict of interest, failure to complete required training (see below), or a

consistent pattern of failure to complete work as assigned or requested by the Administrative Team.

Member Training

Members are required to successfully complete CITI training following appointment to the Board, with refresher training required every three years thereafter. Successful completion requires 80 percent accuracy. CITI training records will be maintained for individual members by the CDOEIRB-C Administrator. Maintenance of other relevant training records, such as attendance at Public Responsibility in Medicine and Research (PRIM&R) conferences and local seminars, is the responsibility of individual members.

Time is also allocated on the agenda during each meeting to educate members and to address current issues and pending changes in regulations. The CDOEIRB-C Chair or members may use this time to disseminate other pertinent or educational information.

CHAPTER 5: INITIAL REVIEW AND APPROVAL

It is DOE policy that all research involving human subjects that falls under the purview of the CDOEIRB-C be reviewed and approved by the CDOEIRB-C prior to the commencement of research tasks involving human subjects. The length of time required to review an application will depend on the PI's timely response to requests by the CDOEIRB-C for additional supporting information, as well as logistical issues such as whether the Board will meet via secure videoconference or teleconference, or in person. Full board meetings are held on the second Wednesday of each month. When needed, additional full board meetings will be added.

All projects under the CDOEIRB-C's purview that are classified (in whole, or in part) must be approved by the DOE IO, following CDOEIRB-C approval and prior to initiation. The DOE/NNSA HSP Program Managers will ensure she receives the appropriate materials (See Attachment IV) to conduct this review.

Initial Review Procedure

Principal Investigator (PI) Develops Draft Research Protocol

The PI develops a draft protocol to conduct research that will involve human subjects or their personal data. The protocol must reflect what will actually occur in the research. The institution is legally responsible (as are researchers and their supervisors) for research conducted at or sponsored by the institution or using the institution's proprietary information. Once the CDOEIRB-C has approved a protocol, the research team is required to follow that protocol and to seek IRB approval for any proposed change before implementing the change. The protocol itself becomes a vital part of official documentation. Should anyone question the research, the approved protocol is powerful evidence that the project has sufficient value to justify the risks or inconveniences involved.

If a proposed study is determined to be human subjects research, the PI must familiarize himself or herself with the information in this manual and must be able to demonstrate that s/he is familiar with:

- His or her responsibilities as a PI
- The CDOEIRB-C procedures described here.

The PI and/or his or her manager review the proposed research and validate the:

- Necessity of involving human subjects
- Scientific merit of the protocol
- Appropriateness of conducting the proposed study at the institutions (or using the institution's funds)
- Source of funding for the protocol

- Safety issues, including potential hazards to research personnel and subjects
- Expertise and experience of members of the research team
- Availability of departmental resources for the proposed work
- Scientific processes involved to minimize potential risk to human subjects.

PI Submits Review Package to CDOEIRB-C Administrator

The review package must include the following:

- Protocol/Application including provisions for the protection of human subjects in accordance with all applicable laws and regulations. Other documents for review may include, but are not limited to, the following:
 - Informed Consent or Information sheet that includes all required elements (see 10 CFR 745.116) and is written in language understandable by the subject population
 - HIPAA release
 - Data use agreement
 - Recruitment materials
 - Advertisements/Outreach materials (flyer, e-mail, phone script, etc.)
 - Surveys/Interviews Scripts/Questionnaires
 - Data collection tools
 - Any external IRB approval letters
 - The complete research/funding application.

CDOEIRB-C Administrator Pre-reviews Submitted Materials

Upon receipt of the protocol package, the CDOEIRB-C Administrator:

- Reviews the package for missing information and items that need clarification.
- Verifies that the package contains all required components
- Gathers enough information to determine whether the proposed project meets the definition of “human subjects research” as defined in the DOE Order 443.1B
- Suggests the level of review required for the study considering the risk/benefit analysis and whether the project is classified, in whole or in part
- Notifies the CDOEIRB-C Chair and the appropriate HSP Program Manager at DOE by email of any proposed HSR that involves the following:
 - an institution without an established IRB
 - a foreign country
 - the potential for significant controversy
 - vulnerable subjects,
 - the generation or use of classified or sensitive unclassified information, or
 - the potential to constitute Human Terrain Mapping (HTM)
- Coordinates with the Chair to assign a designated reviewer for expedited review or adds the review to the agenda for the next meeting of the Full Board
- Distributes complete protocol package to all members participating in the Full Board review; ideally, CDOEIRB-C Members receive the review materials two weeks prior to a scheduled meeting.

Levels of Review

Any project that is classified, in whole or in part, will be considered a classified project by DOE and must be reviewed by the full board. Projects that are unclassified, but intelligence-sensitive, will follow the normal review process outlined in 10 CFR 745/45 CFR 46, and DOE Order 443.1B, as applicable. Projects that are HTM will follow the review process outlined in DOE Order 443.1B. Note that a research project that begins as a full board project or an expedited project may not later become an exempt project.

Full Board Review of Proposed Study.

At the Chair's discretion, a member of the CDOEIRB-C may be assigned as a primary/secondary reviewer for protocols requiring full Board review. Reviewers will perform an in-depth review of all documentation and submit their comments in writing for distribution at the meeting. Other CDOEIRB-C Members will also receive and review the protocol documents. The primary reviewer should have expertise in the area of the protocol being reviewed, but the secondary reviewer should ensure protocols are understandable to all.

At the beginning of each full board meeting, in addition to confirming that they have no conflicts of interest, all CDOEIRB-C Members will be required to sign a non-disclosure agreement (NDA). These NDAs will be maintained in the official meeting files managed by the CDOEIRB-C Administrator. (See p. 35 for additional detail on conflicts of interest.)

During the protocol review, the CDOEIRB-C Administrator documents the deliberations, any issues identified and any conditions that reviewers determine must be met in order to approve the study. The PI may be invited to, or may request to attend the review, or reviewers may call the PI during the review for clarification or additional information as needed. However, the PI cannot participate in or attend the deliberations of the board. The Chair or Administrator also asks for and records the total vote of all eligible voting members.

The CDOEIRB-C evaluates the protocol to ensure that all the requirements for approval, which are specified in detail in 10 CFR Part 745.111 and in 10 CFR Part 745.116, have been satisfied (*see pages 5-10 of this SOP*). Waiver or alteration of informed consent, or waiver of documentation of informed consent, may be considered only in certain instances, as described in 10 CFR Part 745.116(d) and .117, and below:

Waiver or Alteration of Informed Consent

For projects that are not classified, in whole or in part, the CDOEIRB-C may approve a consent procedure that alters some or all of the elements of informed consent, or may waive the requirement to obtain informed consent (or to provide documentation of informed consent), provided the CDOEIRB-C finds and documents in the project records and meeting minutes that the requirements of 10 CFR Part 745.116(d) are met, as follows:

- The research presents no more than minimal risk to the subjects

- The waiver or alteration will not adversely affect the rights and welfare of subjects
- The research could not practicably be carried out without the waiver or alteration, and
- Whenever appropriate, the subjects will be provided with additional pertinent information following their participation (e.g., a fact sheet).

Waiver of Documentation of Informed Consent

An IRB may waive the requirement for the investigator to obtain a signed consent form [45 CFR Part 46.117(c)] for some or all subjects if it finds either of the following to be true:

- 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.
- 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.

Requests for a waiver of documentation of informed consent must be initiated by the PI with the submission of the protocol, citing the criteria in 10 CFR Part 745.117(c) and how the conditions of his/her protocol qualify for each criterion. When the documentation requirement is waived, the Board may require the PI to provide subjects with a written statement regarding the research.

Quorum.

For purposes of the CDOEIRB-C, a voting quorum will consist of a minimum of five CDOEIRB-C Members, including at least one non-scientist, one scientist, and one unaffiliated member. To be approved, proposed research must receive the approval of a majority of those voting members present. Prior to the Board voting, the CDOEIRB-C Chair may ask that any ex-officio representatives with direct programmatic oversight of the project leave the room.

For unclassified projects, if the full board determines that the risk of a study is no more than minimal, the board may change the level of review to expedited. Thus, future reviews of the project will not need full board reviews.

CDOEIRB-C Determination

When the IRB reviews a proposed study, it has four determination options:

- **Approve:** Protocol is approved as submitted, or approved with recommended revisions (without any conditions).

- **Approve with Conditions:** Protocol is determined to require minor modifications or PI must furnish additional information, prior to approval by the CDOEIRB-C to begin the study. At the time when the IRB reviews and approves a research study, the IRB requires as a condition of approval that the investigator: (a) make specified changes to the research protocol or informed consent documents; (b) confirm specific assumptions or understandings on the part of the IRB regarding how the research will be conducted; and/or (c) submit additional documents such that, based on the assumption that the conditions are satisfied, the IRB is able to make all of the determinations required for approval under the Federal regulations at 10 CFR Part 745.111, and if applicable, subparts B, C, or d of 45 CFR Part 46, as well as DOE O 443.1B. With respect to research reviewed and approved with conditions by the IRB at a convened meeting, note that because the IRB is able to make all these determinations, the IRB may designate the IRB Chair (and/or other individual(s) designated by the Chair with appropriate expertise or qualifications) to review responsive materials from the investigator and determine that the conditions have been satisfied, and further review by the IRB at a subsequent convened meeting would not be necessary. *In this case, while the approval date is the meeting date, the effective date of approval is the date on which the Chair has verified that all the conditions have been met.* The PI will be given limited period of time to respond to the IRB's requests, and the human subjects research tasks may not be initiated until the investigator has received written confirmation from the IRB that all conditions have been met. Continuing review must occur within 1 year of the effective date of IRB approval, but the IRB may determine that such continuing review should occur within 1-year of the convened meeting at which the project was conditionally approved, or sooner than that, if the CDOEIRB-C has any concerns about the project.
- **Require Modifications:** Protocol is determined to need major revision or rework before the IRB can complete review and/or the Board has unresolved questions and the PI is not available to address them. The research may not proceed until the IRB reviews the revised research project and approves it at a subsequent convened meeting. Continuing review must occur within 1 year of the convened meeting date at which the project was approved.
- **Disapprove:** Protocol is determined not to meet the minimum criteria required for approval.

Following the IRB's determination, the IRB Administrator creates the applicable determination letter, for review by the Chair. Once approved by the Chair, the Administrator issues it to the PI. The IRB Administrator must verify completion of all required training before the final approval letter for a human subjects research study can be issued.

Approval Period

When the CDOEIRB-C approves a study, it must also establish a schedule for continuing review. The maximum approval period of twelve (12) months is granted to studies that are determined to be no greater than minimal risk. Studies that have potential for greater than minimal risk are evaluated on a case-by-case basis, and review frequency is determined by considering factors such as the health and vulnerability of subjects involved, previously reported adverse events, and investigator/group experience with the proposed work. If the Board deems it necessary to review

a protocol prior to the 12-month maximum, such determination will be explained in the approval letter sent to the PI.

Documentation and Reporting

Investigators cannot initiate research until they have received: 1) documented approval by the CDOEIRB-C of the protocol and all related forms; and, for research that is classified, in whole or in part, 2) documented approval by the DOE IO, on behalf of the Secretary of Energy.

The DOE and NNSA HSP Program Manager will brief the DOE IO on CDOEIRB-C actions by e-mail or in person, on a monthly basis, on the day following each CDOEIRB-C meeting.

Process for Appeal and/or Request for Reconsideration

If a protocol presented at a convened meeting is disapproved or requires modifications, the CDOEIRB-C notifies the PI in writing regarding the issues that need to be addressed for approval. In cases where there is disagreement between the CDOEIRB-C and the PI regarding the nature and extent of the requested changes and these disagreements cannot be resolved amicably in an informal manner, the PI and/or the CDOEIRB-C may appeal to the IO, through the HSP Program Managers, for a review of the matter. The DOE IO may organize a meeting to help facilitate discussion between the CDOEIRB-C, HSP Program Managers, and the PI. The final determination, however, will be made by the CDOEIRB-C, reflecting the Board's autonomy and responsibilities to assure that the risks to human participants involved in research under its purview are minimized and reasonable in relation to the anticipated benefits and to protect the rights and welfare of study participants in accordance with applicable Federal regulations, state laws, DOE directives, and existing ethical principles.

In cases where any member of the CDOEIRB-C does not believe a specific project should be approved by the CDOEIRB-C, that member may appeal to the DOE IO. If the DOE IO affirms the CDOEIRB-C's decision to approve the project, the dissenting CDOEIRB-C member may appeal the CDOEIRB-C's decision to the Secretary of Energy. If the Secretary of Energy affirms the CDOEIRB-C's decision, the CDOEIRB-C member may appeal the CDOEIRB-C's decision to the Director of the Office of Science and Technology Policy (OSTP).

Cooperative Research

[Cooperative research](#) projects involving more than one institution and potentially more than one IRB are permitted under 10 CFR Part 745.114. With the approval of DOE, an institution participating in a cooperative project may enter into a joint review arrangement, may rely upon the review of another institution's qualified IRB, or may make similar arrangements to avoid duplication of effort. When conducting cooperative research, each participating institution is responsible specifically for safeguarding the rights and welfare of the human subjects involved, and an IRB authorization agreement (IAA) (<http://www.hhs.gov/ohrp/assurances>) must be in place. From DOE's viewpoint, however, the CDOEIRB-C will remain the IRB of record for all projects under its purview, and no other IRB within or outside the DOE system may take on that role.

Other Considerations:

International Projects

International projects will be reported to the appropriate HSP Program Manager prior to initiation and will be conducted in conformance with all applicable requirements (e.g., DOE Order 443.1B and 10 CFR Part 745.101(h)).

Research on human subjects must adequately protect the rights and welfare of the subjects regardless of where that research is conducted. All DOE-funded or DOE or DOE site/laboratory-conducted human subjects research that would be subject to US federal regulations and DOE requirements if conducted wholly within the United States, must comply with these requirements even if conducted in other countries.

In addition to IRB review and approval, human subjects research conducted outside the US may involve international and country-specific requirements, including review by the appropriate local equivalent of an IRB. The Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) provides an International Compilation of Human Research Standards. This comprehensive work is updated annually and is a good resource that the CDOEIRB-C should refer to when reviewing projects conducted in other countries.

Research conducted outside the US can also involve a number of additional challenges:

- The IRB must ensure that the proposed research is acceptable in the local setting where it is to be conducted.
- Local community/ethical concerns, subject population, institutional policies and values must be taken into account in addition to the requirements noted above.
- The protocol, informed consent document, and instructions to the foreign IRB (or equivalent) members must be written in the appropriate language and translated into English (for review by the IRB).
- Minutes of the foreign IRB meeting including approval must be translated into English and forwarded to the IRB.
- PIs must be knowledgeable about and sensitive to issues, such as the expectations of the local volunteer population, the practices of the local collaborating experimenter(s), the meaning of informed consent, and possible coercion and enticement activities. Also, the IRB is required to notify DOE about any study that has a foreign component.

To avoid potential delays in IRB review, PIs who are considering international research should contact the IRB Administrator as early as possible in the planning stage to discuss whether additional requirements apply and any attendant time constraints.

Projects Involving Toxic or Potentially Harmful Agents

Using human subjects in research that involves exposure to potentially toxic materials or potentially harmful physical agents (lasers, electromagnetic or particle radiation, noise, heat, chemical tracers, etc.) requires careful consideration. To allow the IRB to fully evaluate the risks

and benefits of the proposed work, PIs must submit information documenting the expected exposure of subjects to these agents, and must have their dose calculations independently reviewed and validated. Any qualified independent party can perform this review, and the PI is responsible for any cost associated with such validation.

The documentation should provide enough information for the IRB to assess the adequacy of the independent validation and must include the following:

- The assumptions used regarding subjects, agent(s) and quantity, route of exposure, and frequency or duration of exposure
- The calculations that yield the estimated dose, and, whenever possible, quantitative risk associated with the exposure
- Reference to any applicable community or occupational standards
- A statement that the reviewer has no direct involvement in the research
- A brief (2- to 4-sentence) summary of the qualifications of the reviewer
- If the proposed subjects are employees at the institutions or a collaborating institution, and the proposed exposure is to chemical agents involving inhalation only, and for which there is an existing OSHA Permissible Exposure Limit (PEL) or American Conference of Governmental Industrial Hygienists Threshold Limit Value (TLV), the analysis may be based on exposure rather than absorbed dose.

Projects involving modification of the human environment (e.g., airflow studies on subways using perfluorocarbon or particulate tracers) will be reviewed by the CDOEIRB-C and managed as human subjects research (see Attachment VII).

Internet Research

- Internet research is any human subjects' research conducted using the Internet. Such research may include two types of information: Publicly Available: Information is publicly available when it is lawfully made available to the general public from: (1) Federal, state, or local government records; (2) Widely distributed media, including information that has been published or broadcast for public consumption, is accessible online to the public, or is available to the public by subscription or purchase; or (3) Disclosures to the general public that are required to be made by federal, state, or local law. Publicly available does not mean "without restriction" (see note below).
- For Authorized Use Only: Information that is restricted to authorized users and governed by specific terms of use and/or data protection rules.

Note: All internet research, regardless of whether information is directly retrieved and/or aggregated for the purpose of the research, must comply with the appropriate DOE directives, such as level of security/classification and protection of personally identifiable information (PII). Only information obtained with due authorizations and that complies with applicable requirements will be approved.

Using Workers as Subjects.

All personnel (employees, contractors, students) are vulnerable to pressures to appear cooperative with regard to projects conducted by their managers and/or co-workers. Additionally, when the subject pool consists entirely of people who are or may be familiar with the study, the validity of the data may be in question.

The basic ethical principles that form the basis of US Federal Laws governing human subjects research are very clear on this topic; subject selection cannot be based solely on the subject's ready availability or malleability. Accordingly, if research plans include recruitment of fellow workers from within the PI's group, justification will need to be included. The following suggestions may reduce the possibility of unintended coercion and concerns about objectivity, while still permitting these individuals to participate as subjects in research:

- IRB-approved advertisements must be posted throughout the site to recruit subjects from a broad base of employees, contractors, and students
- Personal solicitations of co-workers by investigators, or fellow co-workers should be avoided
- A statement should be included about why this isn't a sample of convenience
- Recruitment materials should include how objectivity and validity of the data will be ensured
- Specific steps should be included about how potential coercion will be minimized.

See also Attachment VI.

Investigator Self-Experimentation

Federal Regulations are silent on the matter of researchers who want to participate in their own studies. However, the regulations do not distinguish between self-experimentation and research on people who are recruited for a specific project. As part of its commitment to the protection of the rights and welfare of individuals participating in research, the CDOEIRB-C requires investigators who wish to act as participants in their own studies to submit an application for review and approval following standard procedures outlined in the IRB policies. Though investigator self-experimentation may not raise the conventional ethical concerns outlined in the Belmont Report (<http://www.hhs.gov/ohrp/policy/belmont.html>), all human research projects should undergo ethical review to assure the safety of people involved and the integrity of the research at the institution. While researchers may be aware of the risks of self-experimentation, they may also be more willing to accept risks that are ill-advised. Application for review with the IRB office allows a neutral third party to raise concerns and/or propose measures to promote the welfare of researchers.

HIPAA

The Health Insurance Portability and Accountability Act (HIPAA) governs the way certain health information is collected, maintained, used, and disclosed. It establishes a set of safeguards on certain types of protected health information (PHI). This law affects researchers when proposed research either:

- creates or generates PHI, or
- requires access to and/or use of PHI.

For more information, visit the HHS HIPAA website or contact the CDOEIRB-C Administrator.

The HIPAA Privacy Rule protects the confidentiality of personally identifiable data generated as a result of health care services, and includes the requirement that authorization be obtained in most cases before this type of data can be used for research purposes. The Privacy Rule also requires that research plans involving this type of data be reviewed and approved by an IRB or Privacy Board.

Future Use of Data

Researchers must also consider whether the data generated in the study might be used in future research. If so, that likelihood needs to be communicated to potential subjects in the consent agreement. Otherwise, if researchers later identify a need to use study data for something outside the scope of the original study, or not noted in the consent, they may need to go back and get new consent from subjects before using that data.

Expedited Review Procedure

Note: Expedited reviews cannot be conducted on projects that are classified, in whole or in part. All minimal risk classified projects must be reviewed by the full board. The full board should note that the research is minimal risk and which expedited category it falls into. However, initial and continuing reviews of such research must always be conducted by the full board. Following is the procedure for the expedited review of unclassified projects.

During the pre-review, the CDOEIRB-C Administrative Team documents any issues identified and any conditions that must be met in order to approve the study. The Administrative Team may contact the PI for clarification or additional information as needed. At the Chair's discretion, an additional CDOEIRB-C Member may be designated to assist in the review.

The CDOEIRB-C Administrative Team/designated reviewer evaluates the project in accordance with the requirements for approval (as specified on pages 5 to 10 of this document).

The designated reviewer completes the non-committee review and determines the expedited category.

The CDOEIRB-C has three determination options:

- **Approve:** Protocol is approved as submitted, or approved with recommended revisions (without any conditions).
- **Approve with Conditions:** Protocol is determined to require minor modifications or PI must furnish additional information, prior to approval by the CDOEIRB-C to begin the study. At the time when the IRB reviews and approves a research study, the IRB requires as a

condition of approval that the investigator (a) make specified changes to the research protocol or informed consent documents; (b) confirm specific assumptions or understandings on the part of the IRB regarding how the research will be conducted; or (c) submit additional documents such that, based on the assumption that the conditions are satisfied, the IRB is able to make all of the determinations required for approval under the Federal regulations at 10 CFR Part 745.111, and if applicable, subparts B, C, or d of 45 CFR Part 46, as well as DOE O 443.1B. ***In this case, while the approval date is the date of expedited review, the effective date of approval is the date on which the Chair has verified that all the conditions have been met.*** The PI will be given limited period of time to respond to the IRB's requests, and the human subjects research tasks may not be initiated until the investigator has received written confirmation from the IRB that all conditions have been met. Continuing review must occur within 1 year of the effective date of IRB approval, but the IRB may determine that such continuing review should occur within 1-year of the date of expedited review at which the project was conditionally approved, or sooner than that, if the IRB has any concerns about the project.

- **Require Modifications:** Protocol is determined to need major revision or rework before the IRB can complete review and/or the Board has unresolved questions and the PI is not available to address them. The research may not proceed until the IRB reviews the revised research project and approves it. Continuing review must occur within 1 year of the expedited review date at which the project was approved.

Note: A study cannot be disapproved by the expedited review process. If the designated reviewer and/or Administrative Team is concerned about the project, it should either be sent back to the PI so that he/she can revise the materials and re-submit, or it should be sent for full board review.

Following the CDOEIRB-C's determination, the Administrator creates the applicable determination letter, for review by the Chair. Once approved by the Chair, the Administrator issues it to the PI. The Administrator must verify completion of all required training before the final approval letter for a human subjects research study can be issued.

Procedure for Review of Exempt Human Subjects Research

Note: Exempt reviews cannot be conducted on projects that are classified, in whole or in part. All minimal risk classified projects must be reviewed by the full board. The full board should note that the research is minimal risk and which exempt category it falls into. However, initial and continuing reviews of such research must always be conducted by the full board. Following is the procedure for the review of unclassified exempt projects.

Upon receipt of an application for CDOEIRB-C review, the Administrative Team may determine that the proposed research fits into one of several categories of exempt human subjects research activities (described in 10 CFR 745.101(b)) that may not require expedited or full board review by the CDOEIRB-C. These exempt categories do not apply to research involving (1) deception of subjects where the investigator does not disclose the true purpose of the research

and/or the results of the subject's participation in the study; (2) sensitive behavioral research; or (3) research involving pregnant women or other vulnerable populations.

Following a review by the Administrative Team and determination by the Chair that the research is exempt human subjects research, the Chair may ask that the Administrative Team review the proposed research or may designate another member of the IRB to conduct the review. Although exempt human subjects research does not need to comply with all specific requirements in 10 CFR Part 745, the CDOEIRB-C may impose certain requirements (e.g., use of a consent form) and/or restrictions on the researcher prior to approval. Additionally, like other human subjects research, exempt human subjects research is subject to the reporting requirements in DOE Order 443.1B.

The CDOEIRB-C has four determination options:

- **Approve**: Protocol is approved as submitted, or approved with recommended revisions (without any conditions).
- **Approve with Conditions**: Protocol is determined to require minor modifications or PI must furnish additional information, prior to approval by the CDOEIRB-C to begin the study. At the time when the IRB reviews and approves a research study, the IRB requires as a condition of approval that the investigator (a) make specified changes to the research protocol or informed consent documents; (b) confirm specific assumptions or understandings on the part of the IRB regarding how the research will be conducted; or (c) submit additional documents such that, based on the assumption that the conditions are satisfied, the IRB is able to make all of the determinations required for approval under the Federal regulations at 10 CFR Part 745.111, and if applicable, subparts B, C, or d of 45 CFR Part 46, as well as DOE O 443.1B. *In this case, while the approval date is the date of review, the effective date of approval is the date on which the Chair has verified that all the conditions have been met.* The PI will be given limited period of time to respond to the IRB's requests, and the human subjects research tasks may not be initiated until the investigator has received written confirmation from the IRB that all conditions have been met. Continuing review must occur within 1 year of the effective date of IRB approval, but the IRB may determine that such continuing review should occur within 1–year of the date of the review at which the project was conditionally approved, or sooner than that, if the IRB has any concerns about the project.
- **Require Modifications**: Protocol is determined to need major revision or rework before the IRB can complete review and/or the Board has unresolved questions and the PI is not available to address them. The research may not proceed until the IRB reviews the revised research project and approves it. Continuing review must occur within 1 year of the expedited review date at which the project was approved.
- **Disapprove**: Protocol is determined not to meet the minimum criteria required for approval.

Following the IRB's determination, the IRB Administrator creates the applicable determination letter, for review by the Chair. Once approved by the Chair, the Administrator issues it to the PI. The IRB Administrator must verify completion of all required training before the final approval letter for a human subjects research study can be issued.

Other Considerations When Determining Whether Proposed Research May be Exempt

Existing Data. The term "existing" refers to the time period that the data or material was obtained. "Existing" refers to material or tissue that was "archived" or "on the shelf" prior to approval for the funding of the research. If the data/specimens are collected after approval of the funding, then the data/specimens are not preexisting or "archived," the protocol will require IRB review, and the investigator may be required to obtain written informed consent.

Specimens received as extra material or extra specimens requested from a physician conducting a clinical procedure are not preexisting or "archived" and thus require written informed consent from the subject and review by the IRB. If there is a link to the patient's identity and a possibility that the patient may be contacted in the future, an informed consent document is required. Furthermore, informed consent is required if there is a link to the patient's identity and a possibility that the research may result in commercial or economic value.

Use of existing human biological specimens for genetic research will require review by the IRB. There are additional ethical concerns for genetic research that may not apply for other types of research with biological specimens. Please contact the IRB Office for additional information.

Sensitive Survey Research. Sensitive surveys or questionnaires are seldom exempt from IRB review. A sensitive survey includes questions about illegal activities or highly personal aspects of the subjects' behavior, life experiences, or attitudes. Examples include chemical substance abuse, sexual activity or attitudes, sexual abuse, criminal behavior, sensitive demographic data, detailed health history, etc. The potential for provoking a negative emotional reaction from subjects, their families, or the community is a principal determining factor of sensitive survey research.

Potential for Breaches of Confidentiality. Additional consideration for exemption includes determining if there is a risk associated with a possible breach of confidentiality (i.e., accidental disclosure of drug use to law enforcement personnel). In surveys with potential psychological risk, review for exemption includes risks associated with surveys about sensitive topics as well as those resulting from a breach of confidentiality. When confidentiality is an issue, the presence or absence of subject identifiers may be a decisive factor.

Procedure for the Review of Human Terrain Mapping (HTM)-Specific Requirements

The IRB Administrator learns a proposed project might involve HTM. This information may come from the PI, the research team, the project or program manager, the sponsor, or from other

sources. The IRB Administrator discusses the project with the PI and others, including the Chair, alternate Chair, and Vice Chair, as necessary to gather sufficient information to help determine if it qualifies as HTM. The following DOE requirements are specific to HTM activities:

HTM projects, conducted with DOE funding, or at DOE sites, or by DOE or DOE contractor personnel, whether domestic or international, including classified and proprietary research, shall be strictly limited to only those projects involving the analysis and modeling of de-identified data. Data collection must be done by the sponsor or a non-DOE institution contracted by the sponsor, and the PI can only receive de-identified data directly from the sponsor. Additionally, DOE policy requires that all HTM activities be "managed as human subjects research (HSR)" whether or not they meet the federal definition of HSR.

Statements of work for HTM projects shall be submitted to the DOE/NNSA HSP Program Managers for review and approval prior to initiation. If the project is to be conducted by or for the intelligence community, the Office of Intelligence and Counterintelligence (DOE/IN) must also review and approve it prior to initiation. The HSP Program Manager(s) and DOE/IN shall engage the recognized DOE site IRB, and as needed, the PI and/or sponsor, in clarifying whether the proposed project is HTM and if so, that the data to be used will be de-identified. Additionally, the PI will be asked to provide written verification that only de-identified HTM data will be used.

The IRB will be the only entity authorized to determine whether the HTM data received by the PI after project initiation meets DOE criteria for de-identification.

All SIPP-funded projects, including HTM activities, shall comply with DOE O 481.1C.

If, in the case the sponsor requests assistance in the de-identification of HTM data prior to start of any work on the sponsor's project and/or re-identification of data following completion of the project, DOE sites may provide such services under a separate contract and/or task order with the sponsor by following the appropriate DOE standard operating procedure approved by the DOE Office of Science.

Classification and Disclosure Considerations for all Research Reviewed by the CDOEIRB-C

The lead DOE site that is awarded the contract for the work to be conducted will be responsible for any final classification determinations that are specific to the project, based on the sponsor's classification guide/criteria, if appropriate, and, if any, additional written direction received from the sponsor.

As is stated above, an NDA must be signed by each member of the CDOEIRB-C and any consultants or other DOE representatives to the Board before a review of project materials is conducted. If there are other individuals who should be signing NDAs, the PI must inform the Chair of this requirement.

Each site will follow the general DOE requirements for the management of classified information. i.e., DOE O 471.6, *Information Security*, and other applicable requirements, including those additional requirements that may have been imposed by the subordinate site(s).

The CDOEIRB-C deliberative documents will be marked as "WORKING PAPERS" and will be labeled with the level and category of classification deemed appropriate, such as "SECRET PENDING CLASSIFICATION REVIEW"; and dated. Each page will be so marked at the top and bottom and the documents will have the appropriate cover pages attached and protected at that level. Working drafts will be transmitted among participating CDOEIRB-C members using appropriate media for classified materials (classified fax, classified e-mail, or UPS).

Each iteration of working papers must be dated. If thought to be "secret", the working paper may be held for up to 180 days from that date before classification review/determination by a derivative classifier. If thought to be "top secret", the working paper may be held for up to 30 days before final classification review.

Once the Working Papers are ready to be finalized, the CDOEIRB-C Manager will transmit the draft(s) to the designated derivative classifier(s) at the lead laboratory for the project for final classification review. If there are any disagreements between the lead laboratory and the other DOE sites involved in the development of CDOEIRB-C working documents, the lead laboratory and/or sponsor will make the final classification determination.

Once the classification level has been finalized, all documents will be managed and protected appropriately at that level by all the organizations involved.

Conflict of Interest and Confidentiality

A conflict of interest exists when investigators, CDOEIRB-C Members or consultants and their immediate family members, including spouses, life partners, children, parents, or other dependents, can be shown to have any financial incentive or personal or professional interests that could cause them to lose their objectivity (or create the appearance thereof) in the conduct or

review of research that may, in turn, compromise the validity and integrity of that research and negatively impact the public's trust in DOE's ability to protect human research subjects.

The appearance of a conflict may be just as serious and potentially damaging as a confirmed conflict. Reports of conflicts based on appearances can undermine public trust in irreparable ways even when mitigating facts of a situation are brought to light. Apparent conflicts, therefore, should be evaluated and managed with the same vigor as known conflicts.

Investigators, CDOEIRB-C Members, and DOE management and staff should be aware of the types that exist and report them promptly to the CDOEIRB-C. In all instances the CDOEIRB-C has the authority to make a final determination and take appropriate action, particularly when the rights and welfare of subjects might be impacted.

When the CDOEIRB-C determines that PI has a conflict, it will defer approval until the conflict has been eliminated or resolved. The CDOEIRB-C may take the following action(s):

- Require modifications to the protocol
- Require documentation that the conflict of interest has been eliminated or resolved
- Require assignment of an alternate investigator, and
- Deny approval if the conflict cannot be resolved.

In most instances, modifications or changes to mitigate a conflict of interest must be approved by the convened Board. The convened Board may, at the time of original review, authorize the CDOEIRB-C Administrative Team to approve minor modifications.

Requirements for Conflicted CDOEIRB-C Members

CDOEIRB-C Members are required to notify the Chair or other member of the Administrative Team that a conflict of interest exists prior to reviewing a protocol. They may accomplish this by contacting any member of the CDOEIRB-C Administrative Team prior to the convened meeting or by declaring the conflict at a convened meeting where conflict of interest is addressed as a standing agenda item. In either case, the CDOEIRB-C Chair will notify the CDOEIRB-C at the convened meeting before the protocol review. CDOEIRB-C members with a confirmed conflict of interest must leave the room (cannot participate in the discussion, vote, or be counted toward quorum for the review of the protocol with which they have a conflict of interest). The Chair makes the final determination if there is a conflict of interest, with the exception of a potential conflict of interest for the Chair, which will be put to a vote by the convened Board.

Requirements for Consultants

When consultants are invited to participate in the review of a protocol, a member of the CDOEIRB-C Administrative Team will explain DOE conflict of interest requirements, which include the consultant's responsibility for reporting any potential conflict of interest to the

CDOEIRB-C Chair or other member of the CDOEIRB-C administrative Team. If the CDOEIRB-C administrative Team determines that no conflict of interest exists, the consultant may provide information, pose questions to the investigator, and participate fully in the discussions (though a consultant may never vote). If a conflict of interest exists, consultants will not be invited to participate in the CDOEIRB-C review in any manner.

CHAPTER 6: POST-APPROVAL EVENTS AND ACTIONS

Continuing Review

Federal regulation 10 CFR Part 745.109(e) requires that approved protocols be periodically reviewed to ensure the continuing protection of human subjects over the course of the research. The scheduling of these reviews should be appropriate to the level of risk involved in the study but not less than once every twelve (12) months. Continuing review for projects that are classified, in part or in whole, will be conducted by the full board. The CDOEIRB-C will require that, as part of the application package, the PI submit a copy of signed consent form.

Determination of Which Projects Need Verification from Outside Sources that No Material Changes Have Occurred Since the Last Review. The CDOEIRB-C may determine that some projects need verification from outside sources that no material changes have occurred since the last review. Requiring independent verification may be based on a routine audit plan or any legitimate concern that may include, but is not limited to the following:

- A history of investigator non-compliance
- Complaints from the CDOEIRB-C or subjects that appear not to be adequately addressed by the key research personnel
- Studies where key research personnel have disclosed or failed to disclose significant conflicts
- and/or studies that exhibit high risk profiles.

The details of the independent verification will be worked out on a case-by-case basis but may include conducting an audit before reporting findings.

Expired Protocols. A protocol is considered expired and out of compliance with the terms and conditions of CDOEIRB-C approval if the CDOEIRB-C has not re-approved the protocol prior to the protocol's expiration date. All activities involving subjects must stop until the protocol has been appropriately reinstated, unless the CDOEIRB-C determines that it is in the best interest of the individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration date. Retroactive approval is not allowed under any circumstances.

Continuing Review Approval Date. When the CDOEIRB-C grants approval for one year at the time of each continuing review, and the IRB performs continuing review and re-approves (with or without conditions) the research within 30 days before the IRB approval period expires, the IRB may retain the anniversary of the expiration date of the initial IRB approval as the expiration date of each subsequent one-year approval period.

Continuing Review Procedure

The steps for continuing review and approval are described in detail below. PI submits the continuing review package to the CDOEIRB-C. The review package must include the following:

- Continuing Review Application including provisions for the protection of human subjects in accordance with all applicable laws and regulations (10 CFR 745/45 CFR 46, and DOE Order 443.1B)
- Informed Consent or Information sheet that includes all required elements (see 10 CFR 745.116) and is written in language understandable by the subject population
- Any document in which changes are being requested, and
- When applicable, any external IRB approval letters.

Upon receipt of the continuing review package, the IRB Administrator:

- Reviews package for missing information and items that need clarification
- Verifies that the package contains all required components
- Verifies the study's risk/benefit analysis remains unchanged
- After coordinating with the Chair, assigns a designated reviewer for expedited review, and adds the review to the agenda for the next meeting of the Full board
- Distributes complete protocol package to all members participating in the Full board review; ideally, IRB Members receive the review materials two weeks prior to a scheduled meeting or assigns a designated reviewer if the project is determined to be expedited.

Information to Consider During CDOEIRB-C Review:

When conducting continuing review and evaluating whether research continues to satisfy the criteria for CDOEIRB-C approval of research (as specified on pages 5-10 of this SOP), the IRB should pay particular attention to the following aspects of the research:

- Risk assessment and monitoring – Is there any new information provided by the PI, or otherwise available to the PI, that would alter the IRB's previous conclusion that the risks to the subjects are minimized and the risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects.
- Adequacy of the process for obtaining informed consent- At the time of continuing review, the IRB should review a copy of the informed consent document submitted by the PI to verify that the PI is using the most recently approved version and that the document contains the most accurate, up-to-date information about the research.
- Investigator and institutional issues – When appropriate, the IRB should consider issues such as: changes in the PI's situation or qualifications; complaints related to the conduct of the research; changes in the acceptability of the proposed research in terms of institutional commitments and applicable regulations.

- **Research progress** – The IRB should confirm that the information provided by the PI at the time of continuing review is consistent with the research protocol previously approved by the IRB. If this information suggests that the PI is not conducting the research in accordance with the IRB-approved protocol or the requirements or determinations of the IRB, the IRB should either defer re-approving the research or re-approve the research for a limited period of time and seek explanation from the investigator regarding the apparent discrepancies. The IRB should, as part of its review, also look for any marked difference between the actual and expected rates of enrollment, as well as the number of subjects who discontinued their participation and the reasons for those withdrawals, if known.

Procedure for CDOEIRB-C Full Board Reviews of Continuing Review Package

During the review, the CDOEIRB-C Administrator documents the deliberations, any issues identified, and any conditions that reviewers determine must be met in order to approve the continuation of the study. The PI may be invited to, or may request to attend, the review, or reviewers may call the PI during the review for clarification or additional information as needed. However, the PI cannot participate in, or attend, the deliberations of the board. The Chair or Administrator also asks for and records the total vote of all eligible voting members.

If the full board determines that the risks of a study is no more than minimal, the Board may change the level of review to expedited, and it will not need future review by the Full Board.

CDOEIRB-C Determination

When the IRB reviews a continuing review package for a study, it has four determination options:

- **Approve as submitted** - Protocol is approved as submitted, or approved with recommended revisions (without any conditions)
- **Approve with conditions** - - Study requires additional clarification or minor edits or changes to secure approval. The board, at its discretion, may require that the investigator respond to requested modifications within a specified period. If the response is not received from the PI within the specified time, the application will be considered withdrawn and will be administratively terminated. The IRB must specify whether any conditions need to be satisfied before the PI can continue particular research activities related to those conditions. *Note: since there will be an ongoing study, the date of the convened meeting when the IRB conducts the continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review.*
- **Require modifications** - Protocol is determined to need major revision or rework before the IRB can complete review and/or the Board has unresolved questions and the PI is not available to address them. The research may not proceed until the IRB reviews and approves the revised research project. Continuing review must occur within 1 year of the approval date.
- **Disapprove the research study**: Disapproval of an ongoing study at the time of continuing review usually follows the identification of previously unknown risks to human subjects and typically follows several attempts by the PI, in conjunction with the efforts of the IRB, to

modify study design to afford protection to the subjects. **Note:** Any suspension or termination of IRB approval must be promptly reported to the PI, the appropriate institutional officials, the sponsor, and to OHRP.

The Administrator creates the applicable determination letter and issues it to the PI. The Administrator must verify completion of all required training before the final approval letter for a human subjects research study can be issued.

Process for Expedited Continuing Reviews

Note: Expedited continuing reviews can only be conducted on projects that are not classified, in whole or in part.

During the pre-review, the Administrative Team documents any issues identified and any conditions that must be met in order to approve the continuation of the study. The Administrative Team may contact the PI for clarification or additional information as needed. At the Administrative Team's discretion, an additional IRB member may be designated to assist in the review.

The Administrative Team and/or designated reviewer evaluates the proposal in accordance with the requirements for approval (10 CFR Part 745.111 and .116 (as described on pages 5-10), and determines the expedited or exempt category, or determines that full board review is required.

The IRB may decide, after review of the continuing review application to:

- **Approve as submitted** - Protocol is approved as submitted, or approved with recommended revisions (without any conditions)
- **Approve with conditions** - Study requires additional clarification or minor edits or changes to secure approval. The board, at its discretion, may require that the investigator respond to requested modifications within a specified period. The IRB must specify whether any conditions need to be satisfied before the PI can continue particular research activities related to those conditions. **Note:** *since there will be an ongoing study, the date of the IRB's last continuing review determines the latest permissible date of the next continuing review.*
 - If the response is not received from the PI within the specified time, the application will be considered withdrawn and will be administratively terminated.
- **Require modifications** - Protocol is determined to need major revision or rework before the CDOEIRB-C can complete review and/or the Board has unresolved questions and the PI is not available to address them.

A continuing review package cannot be disapproved by the expedited review process and requires full board review.

Following the IRB's determination, the IRB Administrator creates the applicable determination letter and, after approval by the Chair, issues it to the PI. The IRB Administrator must verify completion of all required training before the final approval letter for a human subjects research study can be issued.

PI-Initiated Modifications to an Approved Protocol

The PI will submit a completed Modification Request form for all proposed modifications or amendments to an approved protocol through classified processes, as appropriate, to the IRB Administrator to initiate IRB review and approval prior to their implementation. The review of modifications for a classified project must be conducted by the full board unless changes are administrative in nature (i.e., changes in project personnel other than the PI, etc.), in which case use of the expedited mechanism may be acceptable. Final determination of the level of review required for each modification will be made by the IRB Chair.

The modification package must include the following:

- The application including provisions for the protection of human subjects in accordance with all applicable laws and regulations
- Any new documents or documents in which changes are being requested.

During the pre-review, the Administrative Team identifies any conditions that must be met in order to approve the modification. The Administrative Team may contact the PI for clarification or additional information as needed. The Administrative Team will also decide whether the modification is minor in nature or major. At the Administrative Team's discretion, an additional IRB member may be designated to assist in the review.

Projects Initially Reviewed by the Full Board

Typically minor modifications are handled by expedited review unless the level of risk to the participants has increased for projects that were reviewed by the full board. Major modifications for studies reviewed by the full board must be returned to the full board.

Projects Initially Reviewed by Using the Expedited Procedure

For unclassified projects that were reviewed by the expedited procedure, review of major and minor modifications can be expedited.

Following review, the IRB Administrator creates the applicable determination letter and issues it to the PI. Note that approving a modification does not change the date of continuing review by the CDOEIRB-C.

Acknowledging CDOEIRB-C Receipt of Supplemental Information Received from PIs

Periodically, PIs may submit miscellaneous documents, such as annual reports, copies of project-related presentations, etc., that have not been specifically requested by the CDOEIRB-C but are relevant to the project. In such situations, the CDOEIRB-C will keep the document(s) on file and respond to the investigator with the following: "Receipt acknowledged. No CDOEIRB-C action needed."

Project Completion/Termination

When a study is completed, the PI must notify the CDOEIRB-C and submit a final report to the Chair.

Deviations from Approved Protocol

The PI may not deviate from an approved protocol without written CDOEIRB-C approval, except when such deviation is necessary to eliminate an immediate hazard to a study subject.

Any member of the project team noting a deviation from an approved protocol is responsible for reporting the deviation or concern to the CDOEIRB-C. The CDOEIRB-C will then review the protocol and any relevant documentation and assess the deviation according to two main criteria:

- Potential or actual harm to the subject and
- Potential or actual effect on the integrity of the study data that affects the risk/benefit ratio of the research.

The CDOEIRB-C will determine whether the incident is a serious violation (a subject was harmed, the potential for harm was created, or the violation compromised the integrity of the study) or non-serious (violation did not harm or potentially harm a subject and does not compromise study integrity).

The CDOEIRB-C will also determine whether further corrective action is warranted:

- If the protocol violation is deemed serious, the CDOEIRB-C will suspend the study.
- If the protocol violation is deemed non-serious, correspondence will be sent from the Chair of the CDOEIRB-C to the PI and the designated institutional representative of the PI's parent institution, directing investigation of the incident (if not already accomplished) and corrective actions.

All findings and conclusions of the CDOEIRB-C will be documented in the protocol file. All the actions outlined above will be conducted in conjunction with all engaged IRBs.

Suspension or Termination of CDOEIRB-C Approval

In accordance with DOE requirements 10 CFR Part 745.113, the CDOEIRB-C has the authority to place on administrative hold, suspend, or terminate approval of research that is not being conducted in accordance with the terms and conditions of the CDOEIRB-C approval (including the requirements for continuing review), or has been associated with unexpected or serious harm to subjects.

Suspension of CDOEIRB-C approval is "a temporary withdrawal of CDOEIRB-C approval for some or all research procedures or a permanent withdrawal of approval for some research

procedures.” Studies that have been suspended still require continuing review. A suspended study may be re-opened after the problem triggering the suspension has been resolved.

Termination of CDOEIRB-C approval is defined as “a permanent withdrawal of CDOEIRB-C approval for all research procedures.” Terminated protocols are considered closed and no longer require continuing review.

Any suspension or termination of CDOEIRB-C approval will be reported promptly to the PI and to his/her line management via a letter that will clearly describe the action and the reasons for the action taken by the CDOEIRB-C. The CDOEIRB-C Administrative Team will also be responsible for reporting to the HSP Program Managers, who will inform the DOE IO. Reporting to OHRP may also be required (<http://www.hhs.gov/ohrp/compliance/reports/>). Issues not resolved within 30 working days will be reported to the appropriate senior DOE official and the research sponsor. Note that:

- The Chair has the authority to suspend a protocol in the situation of a deviation that is serious and
- The advice and recommendations of the full CDOEIRB-C will be addressed once the subjects are no longer at risk.

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CHAPTER 7: UNANTICIPATED PROBLEMS, ADVERSE EVENTS, AND INSTANCES OF NONCOMPLIANCE

When unanticipated problems, adverse events, or instances of non-compliance occur, they must be systematically evaluated, corrected, and reported, as appropriate to the situation. Because the information involved may be classified, DOE O 471.6, *Information Security*, must be followed, unless the required reporting can be done at the unclassified level, which is preferred.

Unanticipated Problems

The phrase *unanticipated problems* involving risks to subjects or others is included, but not defined, in 10 CFR Part 745. During the design of research, investigators carefully consider all possible outcomes that human volunteers may experience in conjunction with the planned protocol. This process forms the basis from which estimates of risk are derived and mitigating actions are planned to minimize the risk. Typically, each of these potential events is included in the protocol narrative; some of these events may in fact be deleterious to the research participant, but not unanticipated. OHRP has published guidance to assist in the identification of unanticipated problems. In general, to be classified as an unanticipated problem, any incident, experience, or outcome should meet all three (3) of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the CDOEIRB-C - approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- 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); and
- Likely to place subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated problems can include loss or compromise of protected health information (PHI) or personally identifiable information (PII), with a loss of privacy or confidentiality for a research participant or others.

Unanticipated problems must be reported as required by 10 CFR Part 745.103(a) and 10 CFR Part 745.103(b)(5).

Adverse Events

Likewise, the term *adverse event* is included, but not defined, in 10 CFR Part 745. In OHRP guidance, the term in general is used very broadly and includes any event meeting the following definition:

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 subjects participation in the research, whether or not considered related to the subject's participation in the research.

Adverse events may encompass both physical and psychological harms. They occur most commonly in the context of biomedical research although, on occasion, they can occur in the context of social and behavioral research. Adverse events must also be reported as required by [10 CFR Part 745.103\(a\)](#) and [10 CFR Part 745.103\(b\)\(5\)](#)

CDOEIRB-C Follow-up with Regard to Unanticipated Problems and Adverse Events:

The CDOEIRB-C has authority, under Federal regulations at 10 CFR Part 745.109(a), to require, as a condition of continued approval by the CDOEIRB-C, submission of more detailed information about any adverse event or unanticipated problem occurring in a research protocol for which it has CDOEIRB-C jurisdiction.

Any proposed changes to a research study in response to an adverse event or unanticipated problem must be reviewed and approved by the CDOEIRB-C and the HSP Program Managers before being implemented, except when necessary to eliminate apparent immediate hazards to subjects. If the changes are more than minor, the changes must be reviewed and approved by a convened meeting of the CDOEIRB-C [[10 CFR Part 745.103\(b\) \(4\)](#) and [10 CFR Part 745.110\(a\)](#)].

Depending on the nature of the unanticipated problem and/or adverse event, the CDOEIRB-C may determine that the project:

- May continue while corrective actions are being taken;
- Must be temporarily suspended until the problem is resolved and/or the protocol rewritten;
or
- Must be terminated. Studies terminated by the CDOEIRB-C must be reported to OHRP.

Noncompliance/Violations/Complaints

All reports of non-compliance, alleged violations of human subjects regulations, and complaints from research subjects will be investigated by the CDOEIRB-C. Substantiated allegations will be forwarded to the CDOEIRB-C Chair for appropriate action as outlined below.

The CDOEIRB-C Chair/HSP Program Managers must immediately report the following to the DOE IO:

- Any serious or continuing noncompliance with the regulations or requirements of the CDOEIRB-C.
- Any suspension or termination of CDOEIRB-C approval for research.
- Any loss of clearance by a PI or other key researcher.

The HSP Program Managers will consult with the sponsor and with the Office for Human Research Protections (OHRP) (http://www.hhs.gov/ohrp/policy/incidreport_ohrp.html) or other appropriate DHHS representative(s) in the OHRP management chain, as needed, given the classification level of the project.

The following minimum information must be included in reports submitted to OHRP:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the CDOEIRB-C project number;
- A detailed description of the incident, experience, or outcome;
- An explanation of the basis for determining that the incident, experience, or outcome represents an unanticipated problem or adverse event; and
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem or adverse event.

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CHAPTER 8: ASSESSMENTS

Research Conduct

During the course of the research, the PI must comply with all CDOEIRB-C decisions, directives, conditions of approval, and the responsibilities described in these guidelines. The CDOEIRB-C may need to contact the PI, or with approval of the participant(s), the participant(s), to evaluate the project's compliance with requirements.

Monitoring Evaluations

The DOE and NNSA HSP Program Managers have the responsibility to both evaluate the CDOEIRB-C itself and also evaluate and monitor researchers to assure that the CDOEIRB-C review and approval process, as well as, the research activities, are in compliance with the applicable regulatory and procedural requirements and conditions of CDOEIRB-C approval. The CDOEIRB-C will conduct a comprehensive self-evaluation at least once in a three-year period using the OHRP Self-Assessment Tool as a guide, and will also be reviewed after the self-assessment is completed, by an external team as part of the review of the DOE HQ HSP.

The DOE and NNSA HSP Program Managers will also annually evaluate a subset of the research activities under its purview (as described below) using the requirements of this SOP, as well as, the applicable DOE and Federal requirements.

PI Evaluation

Every other year, or more frequently if determined necessary by the DOE/NNSA HSP Program Managers, the DOE/NNSA HSP Program Managers will determine which research activities will be evaluated. The selection should be based on relative risk and complexity of the research, and those programs that have demonstrated negative performance in the past and/or have more than minimal risk designation should be reviewed more frequently.

Every effort should be made to coordinate with the PI's home institution to minimize duplicative efforts and disruption to the PI research activities.

For each evaluation that is selected, the DOE/NNSA HSP Program Managers will evaluate compliance with federal and DOE requirements using on-site document reviews, interviews with the PI, staff, and subjects, or a combination as needed to assure a complete review. The results of the evaluation will be submitted to the IO.

During the interactions with the PIs, the DOE/NNSA HSP Program Managers will also ask for feedback on how the PIs believe interactions with the CDOEIRB-C are working and whether the PIs have any suggested improvements for the CDOEIRB-C.

Suggested program elements include:

- Review of study documentation including, but not limited to, determining that unanticipated problems, adverse events, or other instances of non-compliance are reported, protocol amendments are filed with the CDOEIRB-C, etc.;
- Review of the consent process, including documents signed by enrolled subjects;
- Review of processes used to assure PII protections are in place and effective;
- Evaluation of training records for research staff; and
- Other subject areas deemed appropriate by the Chair.

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CHAPTER 9: MEETINGS

Scheduled Meetings

The CDOEIRB-C shall convene monthly at the DOE Forestall Building at 1000 Independence Avenue, SW, Washington, D.C, 20585, in person or in some cases by videoconference. More frequent meetings may be scheduled if required. Videoconference or phone meetings are considered acceptable by [OHRP](#), as long as the voting members have: 1) received all pertinent material prior to the meeting, and 2) can actively and equally participate in the discussion of all protocols. Minutes of such meetings must clearly document that these two conditions have been satisfied in addition to the usual regulatory requirements

After approval by the Chair and Vice Chair, the CDOEIRB-C Administrator will distribute the agenda and all relevant meeting materials to CDOEIRB-C Members prior to the meeting. A Investigators who fail to submit their materials by the required submission date will be scheduled for the next available meeting.

Minutes

The CDOEIRB-C Administrator will take the minutes and submit them to the Chair for approval. Final review by the Board, including any noted modifications will occur at the beginning of the next full Board meeting. Any corrections, modifications, or additions to the minutes will be reported in the next set of meeting minutes. Copies of the approved minutes will also be sent to the DOE IO by the Chair.

Quorum and Voting

A voting quorum is defined as a simple majority of eligible members, which will consist of a minimum of five CDOEIRB-C members, including at least one non-scientist, one scientist, and one unaffiliated member. Should the quorum fail during a meeting (e.g., loss of a majority through recusal of members with conflicting interests or early departures, or absence of a nonscientific member or an unaffiliated member), the CDOEIRB-C may not take officially binding actions or votes unless the quorum can be restored. All voting is conducted in closed session, and voting privileges shall be limited to CDOEIRB-C voting members present at the meeting. Proxy votes are not accepted. The outcome of Board votes is recorded by the CDOEIRB-C Administrator; a majority vote is required for any CDOEIRB-C determination. For clarification, it is possible to lose a quorum during a meeting due to a number of conditions (early departure, conflict of interest, etc.), but a binding action can be taken on any given project if the following conditions are met: 1) there is a quorum at the start the meeting, and 2) the members making up that quorum are present for the discussion, deliberations, and voting on Project X. If the quorum is lost for deliberation and voting on Project Y (for example if one member has a conflict of interest), binding actions will have to be postponed to another meeting for Project Y. However, deliberation and voting on Project Z can still be conducted if that

member and/or enough others to sustain a quorum are present for the discussion, deliberation, and voting on Project Z.

No member may participate in the CDOEIRB-C vote or review of any protocol in which the member has a real or perceived interest or conflicting interest, except to provide information requested by the Board. A CDOEIRB-C Member with any conflict of interest must recuse himself or herself from both the discussion of the project and voting. Such action will be noted in the meeting minutes. Recusals could result in loss of a quorum, in which case voting cannot take place until a quorum has been re-established. If a quorum cannot be re-established, the review of the project or projects must be deferred until the next meeting.

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CHAPTER 10: RECORDKEEPING

CDOEIRB-C Records

All official CDOEIRB-C records will be managed in accordance with DOE O 471.6. During the period of study, any hard copies will be stored by the CDOEIRB-C Administrator in locked file cabinets in a classified space. Following completion of the study, all study-related records will be archived by the CDOEIRB-C Administrator in a secure area. Records for classified projects must be maintained permanently, and records for projects that are not classified should be maintained for a minimum of 10 years.

Protocol Records

The CDOEIRB-C Administrator will assign each protocol a unique, sequential number that indicates the order of receipt. Official CDOEIRB-C records for each protocol include the following that were part of the deliberative process:

- All documentation reviewed by the CDOEIRB-C, including the proposal/funding application and scientific evaluations, if any, that accompany the proposal, any subject recruitment material, questionnaires, a list of any published documents, progress reports submitted by investigators, and reports of any injuries to subjects;
- All correspondence related to the protocol, including e-mail exchanges, that were part of the deliberative process;
- A list of all telephonic communication related to the protocol with a brief summary of the content of each phone call;
- Copies of any press releases related to the protocol that are initiated by the PI;
- Notes from protocol review sessions including reviewer written comments; and
- Approved consent forms, including a copy of a redacted, signed consent form (to be submitted with the continuing review application).

Note: The PI retains all signed consent forms.

Meeting Minutes

Meeting minutes (10 CFR Part 745.115(a)(2) of the CDOEIRB-C meetings shall be taken in sufficient detail to show to following:

- Attendance, including voting members and alternates, invited experts, and any guests present; members absent; and late arrivals or early departures by voting members and/or their alternates;
- Actions taken by the CDOEIRB-C (including listings of exempt and expedited reviews for unclassified projects);
- The vote on these actions, including the number of members voting for, against, and abstaining or recusing;
- The basis for requiring changes or disapproval of proposed protocols;
- A written summary of the discussion of controverted issues and the Board's action; and

Reports of unanticipated problems or adverse events and the action taken by the Board.

Other Official Records

The CDOEIRB- Administrator will maintain the following records, in addition to protocol records and meeting minutes, in compliance with [10 CFR Part 745.115](#) and DOE Order 471.6, *Information Security*:

- As required by [10 CFR Part 745.103\(b\)\(3\)](#), a current membership list that lists members and their areas of expertise, as well as archived rosters;
- Board members' curriculum vitae (CV), at time of appointment and reappointment to the Board;
- Written procedures for the CDOEIRB-C and investigators in the same detail as described in 10 CFR Part 745.103(b)(4) and 10 CFR Part 745.103(b)(5);
- Records of continuing review activities;
- Correspondence between the CDOEIRB-C and the investigators and their local site and institutional IRBs, where appropriate;
- Statements of significant new findings provided to subjects, as required by 10 CFR Part 745.116(b)(5); and
- Reports of unanticipated problems and adverse events and their resolution.

Training Records

Members shall keep documentation of completion of training, as required by the Board. Proof of required training must be furnished to the CDOEIRB-C Administrator, who will maintain a

record of training for each Board member and report to the administrative and HSPP managers if a Board member is out of compliance.

PI Records

The PI must retain all official research records for the length of time as required by law, terms of DOE contract, grant, or cooperative agreement, or as stated in the Federal Register.

CHAPTER 11: REFERENCES

Authority for this Standard Operating Procedure is contained in the following documents:

[10 CFR Part 745, *Protection of Human Subjects*](#);

[45 CFR Part 46, *Protection of Human Subjects*, Subparts B, C, D, and E](#);

[OHRP Guidance on Engagement of Institutions in Human Subjects Research, December 23, 1999](#);

[OHRP Guidance on Reporting Incidents to OHRP, May 27, 2005](#)

[OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007](#);

[OHRP Guidance on Written IRB Procedures, May 16, 2011](#);

[OHRP Guidance Federalwide Assurance \(FWA\) for the Protection of Human Subjects, June 17, 2011](#);

[10 CFR 160, 162, 164 Health Insurance Portability and Accountability Act of 1996 \(HIPAA\)](#);

[Department of Energy Order 443.1B *Protection of Human Research Subjects*](#);

Department of Energy Order 471.6, *Information Security*;

Human Terrain Mapping Data Review Process;

Human Terrain Mapping or Not Human Terrain Mapping; and

Best Practices for Reviewing Classified Human Subjects' Research at DOE Sites.

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CHAPTER 12: DEFINITIONS

Program Manager - The DOE HSP Program Manager and, when an NNSA element is involved, the NNSA HSP Program Manager. (DOE O 443.1B)

Adverse Event - Any unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., 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. (OHRP Guidance, January 15, 2007)

Classified Information - DOE O 471.6, *Information Security*, June 20, 2011, establishes requirements and responsibilities for Department of Energy (DOE) Departmental Elements, including the National Nuclear Security Administration (NNSA), to protect and control classified information as required by statutes, regulation, Executive Orders, government-wide policy directives and guidelines, and DOE policy and directives.

Conditional Approval - Approval of a protocol contingent upon the PI successfully addressing a set of specified concerns identified during any type of protocol review.

Conflict of Interest - Any affiliation or personal, professional, or financial connection with the institution or person submitting a protocol that might create the appearance of impropriety that could undermine confidence in the individual.

De-identified Data - A data set that has no, or limited, identifiers and for which a person with current knowledge of generally accepted scientific principles determines that the risk that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient, has been reduced to the extent practicable. A graded approach must be used in balancing the de-identification of the datasets and the usability of the dataset to accomplish the needed research. (DOE O 443.1B)

Engaged in human subjects' research – Awardee institutions are automatically considered to be “engaged” in human subjects' research whenever:

- They receive a direct award from DOE or other organization to support such research, even where all activities involving human subjects are carried out by a subcontractor or collaborator. The awardee institution is also responsible for ensuring that all collaborating institutions engaged in the research hold an OHRP-approved assurance prior to their initiation of the research. (OHRP Guidance, October 16, 2008)
- The institutions' personnel are involved in the design, analysis of data, or reporting on a human subjects research project, even if the institution receives no funding.

Exculpatory Language – Wording in a consent document in which a volunteer research subject 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. Informed consent may not contain any exculpatory language. Subjects may not be asked to waive, or appear to waive, any of their legal rights, nor may they be asked to release the investigator, sponsor, or institution (or its agents) from liability for negligence. ((OHRP Guidance, November 15, 1996;)10 CFR 745.116)

Federal-wide Assurance – The Federal Policy (Common Rule) for the protection of human subjects requires that each institute “engaged” in Federally-supported human research file an “assurance” of protection for human subjects. The assurance formalizes the institution’s commitment to protect human subjects. The requirement to file an assurance includes both “awardee” and collaborating “performance site” institutions. (OHRP Guidance June 17, 2011);

HIPAA – Health Insurance Portability and Accountability Act of 1996, Public Law 104-191, a foundation of Federal protections for the privacy of protected health information. (45 CFR 160, 162, 164)

Human Subjects Research (HSR). (DOE O 443.1B) - Any systematic investigation (including research development, testing, and evaluation) involving intervention or interaction with individuals or using their personally identifiable information or materials, designed to develop or contribute to generalizable knowledge². In addition to traditional biomedical and clinical studies, such research includes but is not limited to studies that—

- use humans to examine devices, products, or materials with the express purpose of investigating human-machine interfaces or evaluating environmental alterations when humans are the subjects being tested;
- use personally identifiable bodily materials such as cells, blood, tissues, urine, or hair, even if the materials were collected previously for a purpose other than the current research;
- collect and use personally identifiable information such as genetic information or medical and exposure records, even if the information was collected previously for a purpose other than the current research;
- collect personally identifiable or non-identifiable data, surveys, or questionnaires through direct intervention or interaction with individuals; and
- search for generalizable knowledge about categories or classes of subjects (e.g., linking job conditions of worker populations to hazardous or adverse health outcomes).

² New information that has relevance beyond the population or program from which it was collected or information that is added to the scientific literature.

Human Terrain Mapping - 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 Human Terrain Mapping (HTM), such activities are often referred to as human social culture behavior (HSCB) and human terrain systems (HTS) studies. It is DOE policy that HTM activities will be managed as HSR. (DOE O 443.1B)

Informed Consent – A person’s voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or undergo a diagnostic, therapeutic, or preventive procedure. It is obtained after providing the subject with the basic elements of informed consent as set forth in 45 CFR Part 46 and 10 CFR Part 745. Informed consent documents shall include disclosure of all potential risks and related consequences or adverse effects, as well as any benefits that may occur as a result of such participation. In giving informed consent, participants may not waive or appear to waive any of their legal rights, or release or appear to release the investigator, the sponsor, the institution or agents thereof from liability for negligence. (10 CFR 745)

Internet research is any human subjects’ research conducted using the [Internet](#). On the internet are two types of information: *publicly available* and *for authorized use only*.

- **Publicly Available**: Information is publicly available when it is lawfully made available to the general public from: (1) Federal, state, or local government records; (2) Widely distributed media, including information that has been published or broadcast for public consumption, is accessible online to the public, or is available to the public by subscription or purchase; or (3) Disclosures to the general public that are required to be made by federal, state, or local law. Publicly available does not mean “without restriction” (see note below).
- **For Authorized Use Only**: Information that is restricted to authorized users and governed by specific data protection rules.

Note: All Internet research, regardless of information type, must comply with the appropriate DOE directives, such as level of security/classification and protection of personally identifiable information (PII). Only information obtained with due authorizations and that complies with applicable requirements will be approved by DOE.

Legally Authorized Representative – An individual, judicial or other body authorized under applicable law to give consent on behalf of a prospective subject for the subject’s participation in the procedure(s) involved in the research. (10 CFR 745)

Minimal Risk – 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. (10 CFR 745)

Noncompliance – Failure of a person, group, or institution to act in accordance with Federal and DOE requirements.

The Office for Human Research Protection (OHRP) – The Department of Health and Human Services oversight body that provides guidance and oversight to organizations overseeing and conducting research and to their IRBs.

Ongoing Study/Project – A study/project previously reviewed and approved by the CDOEIRB-C.

Principal Investigator (PI) – The lead researcher who was designated by his or her site senior management for the overall management of the project.

Private Information – This 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 that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record). Such 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 collection of the information to constitute research involving human subjects. (10 CFR 745)

Protected Health Information (PHI) –(HIPAA) - This means identifying information about an individual in oral or recorded form, if the information:

- relates to the physical or mental health of the individual, including information that consists of the medical history of the individual's family;
- relates to the providing of health care to the individual, including the identification of a person as a provider of health care to the individual;
- is a plan of service within the meaning of the Long-Term Care Act, 1994 for the individual;
- relates to payments or eligibility for health care with respect to the individual;
- relates to the donation by the individual of any body part or bodily substance of the individual or is derived from the testing or examination of any such body part or bodily substance;
- is the individual's health number; or
- identifies an individual's substitute decision-maker.

Personally Identifiable Information (PII) – Any information collected or maintained about an individual, including but not limited to, education, financial transactions, medical history and criminal or employment history, and information that can be used to distinguish or trace an individual's identity, such as his/her name, Social Security number, date and place of birth, mother's maiden name, biometric data, and any other personal information that is linked or linkable to a specific individual. (DOE O 443.1B)

Information regarding Federal and DOE requirements for the protection of PII of human research subjects and DOE employees is included in Attachment I.

Identifiable Private Information - Any information that would allow an investigator to readily ascertain the identity of an individual, using: 1) information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place; and/or 2) information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public. The following are examples of types of information are considered identifiable private information by OHRP:

- Name;
- Facial images;
- Social security number; and
- Voice recordings.

Therefore, any research involving the above is considered human subjects research.

Quorum – A simple majority of eligible voting Board members, which will consist of a minimum of five CDOEIRB-C members, including at least one non-scientist, one scientist, and one unaffiliated member. (DOE Policy)

Research – A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this document, whether or not they are conducted or supported under a program that is considered research for other purposes. (10 CFR 745)

(Note: Generalizable, in classified research, should be viewed in terms of its contribution to knowledge within the intelligence community and/or the scientific contribution to the specific field of study.)

Serious Adverse Event (FDA Guidance, January 10, 2014) - Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- Results in death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect; and
- Any other adverse event that, 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. Examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood

dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Serious Noncompliance – Failure of a person, group, or institution to act in accordance with Federal and DOE requirements, and/or requirements in this SOP, such that the failure could adversely affect the rights, safety, or welfare of a human subject; place a human subject at increased risk of harm; cause harm to a human subject; affect a human subject’s willingness to participate in research; or damage or compromise the scientific integrity of research data.

Unaffiliated Member - For purposes of the CDOEIRB-C, an unaffiliated member is an individual who is not currently a federal or DOE laboratory employee. (DOE Policy)

Unanticipated Adverse Event (OHRP Guidance, January 15, 2007) – Any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either

- (1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- (2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event.

Unanticipated Problem (DOE O 443.1B) – In general, to be classified as an unanticipated problem, any incident, experience, or outcome should meet all three of the following criteria:

- 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;
- Related or possibly related to the 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); and
- Likely to place subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Vulnerable Populations - Populations identified in Subparts B, C, and D of 45 CFR Part 46: pregnant women, children, and prisoners. Also, as a matter of policy, DOE considers its current and former workers to be a vulnerable population (Attachment VII) and subject to some of these provisions, as approved by the management, in consultation with the IO

Attachment I.

DOE Institutional Review Board Template for Reviewing Human Subjects' Research Protocols that Utilize Personally Identifiable Information

The following items must be addressed in all protocols:

1. Keeping PII confidential.
2. Releasing PII only under a procedure approved by the responsible IRB(s) and DOE, where required.
3. Using PII only for purposes of the Former Worker Medical Screening Program, assisting participants filing claims under the Energy Employees Occupational Illness Compensation Program (EEOICP), or with the consent of the participant.
4. Handling and marking documents containing PII as "containing PII or PHI".
5. Establishing administrative, technical, and physical safeguards to prevent unauthorized use or disclosure of PII.
6. Making no further use or disclosure of the PII except when approved by the responsible IRB(s) and DOE, where applicable, and then only under the following circumstances: (a) in an emergency affecting the health or safety of any individual; (b) for use in another research project under these same conditions and with DOE written authorization; (c) for disclosure to a person authorized by the DOE program office for the purpose of an audit related to the project; (d) when required by law; or (e) with the consent of the participant.
7. Protecting PII data stored on removable media (CD, DVD, USB flash drives, etc.) using encryption products that are Federal Information Processing Standards (FIPS) 140-2, *Security Requirements for Cryptographic Modules*, certified.
8. Using passwords to protect PII used in conjunction with FIPS 140-2 certified encryption that meet the current DOE password requirements.
9. Sending removable media containing PII, as required, by express overnight service with signature and tracking capability, and shipping hard copy documents double wrapped.
10. Encrypting data files containing PII that are being sent by e-mail with FIPS 140-2 certified encryption products.
11. Sending passwords that are used to encrypt data files containing PII separately from the encrypted data file, i.e., separate e-mail, telephone call, separate letter.
12. Using FIPS 140-2 certified encryption methods for Web sites established for the submission of information that includes PII.

13. Using two-factor authentication for logon access control for remote access to systems and databases that contain PII (two-factor authentication is contained in the National Institute of Standards and Technology (NIST) Special Publication 800-63 Version 1.0.2, *Electronic Verification Guide*, found at http://csrc.nist.gov/publications/nistpubs/800-63/SP800-63V1_0_2.pdf).
14. Reporting the loss or suspected loss of PII immediately upon discovery to (1) the DOE funding office program manager, and (2) the applicable IRBs (as designated by the DOE program manager); if the DOE program manager is unreachable, immediately notify the DOE-CIRC (1-866-941-2472, www.doecirc.energy.gov).

Attachment II. CDOEIRB-C Membership Roster

July 2015

CDOEIRB-C Administrator: Terri Loveless, Office of Intelligence and Counterintelligence

MEMBER'S NAME	EDUCATION	AFFILIATION	EXPERTISE
Laura Brosch	RN; MSN and PhD-Nursing	Director, Office of Research Protections, Army Medical Materiel Command	Nursing; Human Subjects Protection
Mark Elmore	BS-Computer Science; MBA	Retired scientist from Oak Ridge National Laboratory	Computer science, particularly large scale computing and big data obfuscation, de-identification, replication, and surrogation Unaffiliated Member
Jessica Graff	BS-Computer Science	Senior Cyber Security Analyst, Office of Intelligence and Counterintelligence, DOE	Cyber Security
Jeffrey Halick	BS-Business Administration; MS-Information Systems; MS-National Security Strategy	NSA SIGINT Representative; Detailee to the DOE Office of Intelligence and Counterintelligence	National Security; Intelligence Planning and Analysis; Program Management (<i>non-scientist</i>)
Neil Hornung	BA-Criminal Justice; MA- Public Policy; MS-Defense Resource Management	Branch Chief, Technology Protection Branch, Threat Assessments Division, Office of Intelligence and Counterintelligence	Supply Chain Risk Management; Counterintelligence; Criminal Investigation (<i>non-scientist</i>)
Leila Langston,	BA-Political Science	Director, Analytic Support Division, Office of Intelligence and Counterintelligence	Human Intelligence (HUMINT) Collection and Analysis; Management (<i>non-scientist</i>)
Patrick McNeilly,	PhD-Pharmacology	Senior Health Policy Analyst, FDA (previously with the OHRP Compliance Division)	Pharmacology; Public Health, Human Subjects Protection; Member of the Public Health Service
Jim Morris,	PhD-Microbiology	Consultant; Research Scientist, Emeritus, Pacific Northwest National Laboratory(PNNL); Former Chair of the PNNL IRB and Current Chair of the Central DOE IRB (unclassified)	Microbiology/Immunology; Human Subjects Protection Unaffiliated Member
Paul Morrison	MS-Systems Engineering	Office of Intelligence and Counterintelligence	Nuclear Weapons RDT&E
John Ordaz,	BS-Chemical Engineering; Professional Engineer	National Nuclear Security Administration; NNSA HSP program manager	Engineering; Human Subjects Protection; Chair
Roxanne Reisman	,AAS-Business Analysis; Pursuing	DOE Office of Intelligence and Counterintelligence, Office of	Business Analysis/Vice Chair (<i>non-scientist</i>)

July 2015

	Additional Degree in Equine Science	the Deputy Director	
Alfredo Sancho	MS-Human Parasitology; PhD-Pharmaceutical Science; MPH-Epidemiology and Mental Health	Office for Human Research Protections; Compliance Division	Human Parasitology, Pharmaceutical Sciences; Human Subjects Protection; Public Health; Member of the Public Health Service
Elizabeth (Libby) White	BA-Japanese; MBA; MPH; CIP	DOE Office of Science; DOE HSP Program Manager	Public Health; Human Subjects Protection; Alternate Chair

Attachment III. References

10 CFR Part 745, *Protection of Human Subjects*, Department of Energy; identical to 45 CFR 46 Subpart A

10 CFR Part 745.103, *Assuring compliance with this policy—research conducted or supported by any Federal department or agency*

10 CFR Part 745.109, *IRB Review of Research*

10 CFR Part 745.110, *Expedited Review Procedures for Certain Kinds of Research Involving no More Than Minimal Risk, and for Minor Changes in Approved Research*

10 CFR Part 745.115, *IRB Records*

10 CFR Part 745.116, *General Requirements for Informed Consent*

45 CFR Part 46, *Protection of Human Subjects*, Public Welfare, Department Of Health and Human Services

DOE Order 443.1B, *Protection of Human Research Subjects*, March 17, 2011

DOE Order 471.6, *Information Security*, June 20, 2011

FIPS 140-2, *Security Requirements for Cryptographic Modules*, Federal Information Processing Standards Publication, December 3, 2002

NIST Special Publication 800-63, Version 1.0.2, *Electronic Authentication Guideline*, National Institute of Standards and Technology, April 2006

The Nuremberg Code, Reprinted from *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*, Vol. 2, pp. 181-182. Washington, D.C.: U.S Government Printing Office, 1949

The Declaration of Helsinki, World Medical Association (WMA), October 2008 (latest version should be cited)

The Belmont Report, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979

Attachment IV

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DOE Approvals Following Central DOE Institutional Review Board-Classified Review and Approval

Project Title

Is the project, in whole or in part, classified _____ (Whole/Part)?

If yes, highest level _____

IRB Initial Approval Date _____

Level of risk: _____ (MR, MIMR, OMIMR) (Use: MR - no more than minimal risk; MIMR - minor increase over MR; OMIMR - more than a minor increase over MR)

Appropriate Human Subjects Protection Program (HSPP) Manager _____ (NNSA or DOE)

Note: The Institutional Official (IO), on behalf of the Secretary of Energy, will approve classified Human Subjects Research projects unless the IO determines that elevation is needed.

_____ IN Manager	_____ Recommended Level (IO/US/S)	_____ Date
_____ NNSA HSPP Manager	_____ Recommended Level (IO/US/S)	_____ Date
_____ DOE HSPP Manager	_____ Recommended Level (IO/US/S)	_____ Date

Institutional Official Determination:

Comments _____

Approval Level Required (IO/US/S) _____ Date _____

Institutional Official

Attachment V

Memo from DOE IO to DoD Documenting the Process for Second Tier Review of Certain DoD-funded Projects

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Department of Energy
Washington, DC 20585

February 10, 2015

MEMORANDUM TO: ^{Pst} PATRICK MASON, DIRECTOR FOR HUMAN PERFORMANCE, TRAINING, AND BIOSYSTEMS, OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE FOR RESEARCH AND ENGINEERING

FROM: SHARLENE C. WEATHERWAX, DOE INSTITUTIONAL OFFICIAL FOR HUMAN SUBJECTS RESEARCH AND ASSOCIATE DIRECTOR OF SCIENCE FOR BIOLOGICAL AND ENVIRONMENTAL RESEARCH *Sharlene Weatherwax*

SUBJECT: Department of Energy (DOE)-Conducted Research Involving Human Subjects

Thank you for presenting an alternate path for the final review of projects Tristan, Hat Trick, and Helios. These DOE-conducted projects are awaiting initiation because the specific Department of Defense (DoD) Component funding these projects (referred herein as "Sponsor") is undergoing the revision of (and submission to your office) their DoD required documentation to reflect changes in DoD policy (DODI 3216.02).

Projects Tristan, Hat Trick, and Helios will be conducted by a DOE laboratory (Oak Ridge National Laboratory (ORNL)), at a DOE facility, and with non-DoD subjects. No DoD personnel will be engaged* in the human subjects research. These projects have been reviewed and approved by the Central DOE Institutional Review Board-Classified (CDOEIRB-C).

While the Sponsor revises its DoD documentation, DOE will assume responsibilities associated with the protection of human subjects as described below:

- Until otherwise notified by your office, DOE Headquarters will take responsibility for any second-tier reviews (i.e. Headquarters Level Reviews (HLR) or Component Level Reviews (CLR)) required by DOE or DoD policy.
 - o The DOE Headquarters review, following the CDOEIRB-C approval, includes: 1) review/concurrence by the DOE Human Subjects Protection Program (HSPP) Manager, the National Nuclear Security Administration (*semi-autonomous part of DOE*) HSPP Manager, and the HSPP lead in the DOE Office of Intelligence; and 2) approval by the DOE Institutional Official (IO).
 - o Note: Both DOE Headquarters and ORNL have Federalwide Assurances.
- DOE will adhere to all applicable requirements for DoD-supported research involving human subjects conducted by another Federal Department which has adopted the "Common Rule."
- DOE may contact your office directly should any assistance be required with the adherence or implementation of DoD-unique requirements. DOE may notify the Sponsor of communications with your office should the Sponsor or DOE deem such notification necessary.

* Per OHRP Guidance on Engagement of Institutions in Human Subjects Research (October 16, 2008), an institution is considered *engaged* in a particular non-exempt human subjects research 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.

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- Any non-compliance, adverse event, or unanticipated problem related to the above projects will be investigated by DOE Headquarters and reported to DoD – both your office and the sponsoring component's office.
- You and I will meet either in person or by phone, at least annually, to discuss the status of these projects and the implementation status of the sponsoring component's efforts to set up its HSPP.

Should this Sponsor request that ORNL, any other DOE laboratory, any DOE Federally Funded Research and Development Center (FFRDC), or DOE University Affiliated Research Center (UARC), conduct additional projects during this interim period, DOE Headquarters and the Sponsor will notify your office in writing prior to the start of the review/approval process described above.

We look forward to our continued work with your office on this important program.

cc:

Joseph Cohn, DoD, Deputy Director, Human Performance Training and BioSystems Directorate
Heather McCreary, DoD, Human Performance Training and BioSystems Directorate
Thom Mason, ORNL IO
Leigh Greeley, ORNL HSPP Coordinator
Elizabeth White, DOE HSPP Manager
John Ordaz, NNSA HSPP Manager
Lachelle Barney, IN, Director, SIPP Programs and IN HSPP lead
Jim Morris, Chair, Central DOE IRB-C
Terry Reser, Vice Chair, Central DOE IRB-C
Elliot Oxman, DOE/GC
Chris Boehnen, ORNL PI
Hector Santos-Villalobos, ORNL PI

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Attachment VI
Policy Memo from DOE IO Considering Current or Former
DOE and M&O Contractors Vulnerable Subjects



Department of Energy
Washington, DC 20585

May 22, 2015

Dear Laboratory Institutional Officials:

The purpose of this communication is to remind DOE sites that DOE considers current or former Federal or contractor employees who become subjects of DOE human subjects research (HSR) to be vulnerable subjects. DOE HSR includes all HSR conducted with DOE funding, at DOE institutions, or by DOE or DOE contractor personnel.

As is stated in the DOE Report, [Creating an Ethical Framework for Studies that Involve the Worker Community](#), "when workers are the subjects of research, additional care must be exercised to assure that their participation is truly voluntary and that data collected about individual workers are kept confidential....For consent to be informed, participants must have adequate, understandable descriptions of the study purpose, what is expected of them, and any benefits and risks they may experience. For consent to be voluntary, they must not face coercion or reprisal for their decisions."

Many ongoing projects at DOE sites involving employees as subjects are work-for-others projects that may be sensitive in nature and require that information be close held. It is especially important with these projects to ensure that employees who participate as subjects do so without undue influence or potential repercussions.

Most of your sites already have policies in place to protect employees who become research subjects. New researchers should be informed of these policies and IRBs should be reminded that, in ensuring that the *Criteria for IRB approval of research (as stated in 10 CFR Part 745.111)* are met prior to approving HSR protocols, they should place special emphasis on 10 CFR 745.111 (b) if employees are research subjects.

Section 10 CFR Part 745.111(b) states: "When some or all of the subjects are likely to be vulnerable to coercion or undue influence...additional safeguards have been included in the study to protect the rights and welfare of these subjects."

Please feel free to contact me or the HSP Program Managers with any questions:

Elizabeth (Libby) White, DOE HSP Program Manager:
elizabeth.white@science.doe.gov; 301-903-7693

John Ordaz, NNSA HSP Program Manager:
john.ordaz@nnsa.doe.gov; 202-586-0142

2

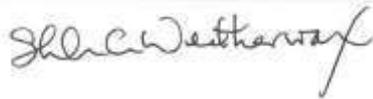
Sincerely,



Elizabeth (Libby) White
DOE HSP Program Manager, SC-23.2



John Ordaz
NNSA HSP Manager, NA-50

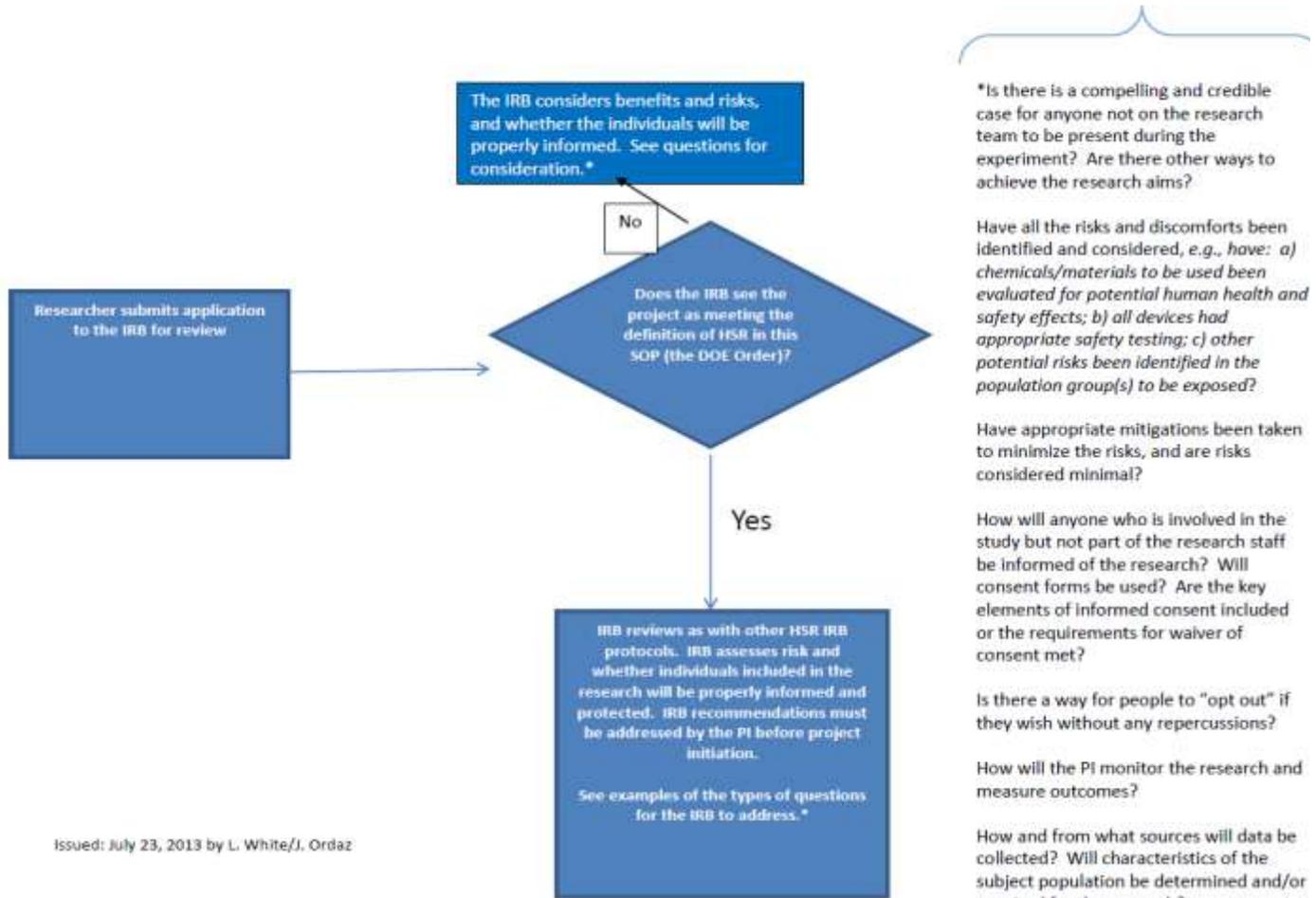


Sharlene C. Weatherwax, Ph.D. DOE
Institutional Official for Human Subjects
Research
Associate Director of Science
for Biological and Environmental Research

cc:
Lachelle Barney, IN-10
Roxanne Reisman, IN-1
Mary Fields, AU-10
Isaf Al-Nabulsi, AU-10
DOE Laboratory IRB Chairs
DOE Laboratory IRB Managers
Central DOE IRB Chair and Vice Chairs
Managers, DOE Site Offices

Attachment VII

Flowchart - DOE Expectations for Research Involving Intentional Modification of the Human Environment



Issued: July 23, 2013 by L. White/J. Ordaz

BACK COVER