OAK RIDGE SITE-WIDE INSTITUTIONAL REVIEW BOARD

STANDARD OPERATING PROCEDURE

PURPOSE, BACKGROUND, AND AUTHORITY

The institutional authority under which the IRB is established.

Oak Ridge Associated Universities (ORAU) has established and will maintain the Oak Ridge Site-wide IRB (ORSIRB) in accordance with the DOE Order 443.1B and 10 CFR 745/45 CFR 46. The ORSIRB will review and oversee research conducted at participating sites within the purview of the Department of Energy (DOE) Oak Ridge Operations (ORO) to assure that it meets ethical principles and complies with federal regulations that pertain to human subject protection.

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

The purpose of the IRB

The ORSIRB is responsible for protecting the rights and welfare of human subjects in research conducted using DOE funds, facilities, or personnel at the participating institutions. The ORSIRB must review all such research protocols and shall comply with applicable DOE Directives and pertinent federal, state, and local laws and regulations.

The institutions under the purview of the ORO that are engaged in human subjects research (HSR) are expected to establish policies in accordance with the DOE Order 443.1B and 10 CFR 745/ 45 CFR 46. These institutions must also obtain a Federalwide Assurance (FWA) with the Office of Human Research Protection (OHRP) under the Department of Health and Human Services (DHHS) and designate the ORSIRB as the IRB of record. Institutions submitting proposals to the IRB are expected to acknowledge and accept their responsibilities for protecting the rights and welfare of human subjects in research covered by this assurance. It is the policy of the ORSIRB to not defer to collaborating institutions except on a case-by-case basis.

A copy of ORAU's FWA will be maintained in the Human Research Protection Program Office.

The principles that govern the IRB

The ORSIRB is guided by the ethical principles set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, entitled "Ethical Principles and Guidelines for the Protection of Human Subjects in Research" (the Belmont Report). These three principles are autonomy, beneficence, and justice.

Autonomy means "respect for persons." It 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. Autonomy further requires protection of subject privacy, confidentiality of data, and increased protection for vulnerable populations.

Additionally, the credibility of any IRB is tied directly to its independence within the institution where it is housed. This autonomy is essential to avoid even the perception of undue influence by either institutional management or the community of researchers within the institution.

Beneficence requires that researchers (and their institutions) do no harm. This includes minimizing the nature, probability, and magnitude of risk while maximizing potential benefits.

Justice requires that the benefits and burdens of research be distributed fairly. Subjects should be recruited based on their relation to the problem being studied 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 without justification.

The ORSIRB assures that where applicable, research complies with state and local laws, regulations, and institutional policies that relate to research involving human subjects. Additionally, the ORSIRB complies with any other federal and state regulations and statutes which apply to research under its jurisdiction, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

The ORSIRB may, at its discretion, consider other ethical guidelines as well, including those set forth in the Nuremberg Code, the Declaration of Helsinki, the International Conference on Harmonization, professional society codes of ethics and reports and recommendations from national advisory bodies, such as the National Bioethics Advisory Commission (NBAC) and the Secretary's Advisory Committee on Human Research Protections (SACHRP).

THE AUTHORITY OF THE IRB

The scope of authority is defined, that is, what types of studies must be reviewed.

These policies apply to all research activities that involve human subjects (even if the research team are the only subjects) according to the DOE Order 443.1B, 10 CFR 745 and 45 CFR 46, regardless of funding source. These studies include, but are not limited to, studies that are:

- Conducted or sponsored by participating institutions.
- Conducted or directed by any employee or agent of these institutions in connection with his or her institutional responsibilities.
- Conducted or directed by any employee or agent of these institutions using any property or facility of these institutions or involve the use of information by these institutions to identify or contact human research subjects or prospective subjects.
- In accordance with the DOE Order 443.1B, DOE requires that Human Terrain Mapping (HTM), also known as Human Social Cultural Behavioral (HSCB) research, and intentional modification of an individual's or a group of individuals' environment be managed as human subjects research.

Authority to disapprove, modify, or approve studies based on consideration of human subject protection aspects.

According to 10 CFR 745.109(a) an IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

According to 10 CFR 745.109(e) an IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

Authority to require progress reports for the investigator and oversee the conduct of the study (or that require special monitoring).

Continuing review at least once a year is required for all research studies, including exempt studies, under ORSIRB oversight at intervals appropriate to the magnitude of risk of the project and other considerations.

The ORSIRB may, at its discretion, perform monitoring or request monitoring of a project or analyses of interim reports such as adverse events and audit reports, in addition to that accomplished through initial, amendment, and annual continuing reviews. For example, the IRB may choose to undertake extra monitoring for research that presents greater than minimal risk or to gauge the progress of recruitment for vulnerable subjects or to follow the research progress on controversial subject matter. The IRB may also consider the frequency and nature of adverse events reported to-date.

The IRB may also choose to monitor one or more of the projects of a single investigator in consideration of the experience of the investigator or as follow-up to previous reports of complaints or non-compliance or prior IRB interactions with the individual.

Examples of Special Monitoring

Monitoring may include, but is not limited to:

- Shortened approval periods and/or interim, scheduled reports from the investigator during the approval period.

- Site visits to research locations.
- Interviews of subjects.
- Third party witness to the informed consent process.
- Review of research records.
- Independent, third-party monitoring to confirm that no material changes in the study have occurred.

The IRB shall communicate with investigators, as appropriate, regarding the outcomes of these additional monitoring efforts. The communication from the IRB will come in the form of a formal letter when necessary.

Authority to suspend or terminate approval of study or impose restrictions.

Only the convened board is authorized to suspend or terminate research.The ORSIRB may suspend or terminate approval of research following appropriate review and deliberation by the convened board for any of the following reasons:

- The research is not being conducted in accordance with IRB requirements.
- The research has been associated with unexpected harm to subjects.
- The risks to subjects cannot be minimized or a favorable risk-benefit ratio cannot be maintained.
- Any suspension or termination of approval or restriction under this provision shall include a statement of the reasons for the action and inform the Principal Investigator of institutional notification and reporting requirements.

Key Definitions:

Suspension of Research Activity –The temporary withdrawal of IRB approval for a human subjects research project or discontinuing a Principal Investigator's privilege to conduct human subjects research. The suspension may be partial, in that certain activities may continue while others must stop, or it may be complete, in that no activity related to the research may proceed.

Termination of Approval –The ending of all activities related to a human research project or a principal investigator's privilege of conducting the research except for the continuation of follow-up activities necessary to protect human subject safety.

Restrictions on a study –Suspension or termination of a portion of a study found in non-compliance either permanently or until it is brought into compliance.

RESPONSIBILITIES AND RELATIONSHIPS

Institutional Official (IO)

The President or Director of each participating institution or their officially appointed delegate is responsible for human subjects protection at their site. This Institutional Official (IO) has the following responsibilities:

- Sets the "tone" for institutional culture of respect for human subjects.
- Certifies compliance with federal policies and the DOE Order 443.1B to DOE Headquarters (HQ) Office of Science (SC) Human Subjects Protection Program (HSPP) Manager.
- Encourages and promotes communication among staff and management as a means of maintaining a high level of awareness regarding protecting the rights and welfare of human subjects.
- Officially delegates IO responsibility to another individual, if so desired
- Encourages participation in human subjects educational activities.
- Supports IRB authority and decisions.
- Appoints Chair of the IRB.
- Removes IRB member for cause.

Research investigators

The Research Investigator ensures that proposals for studies, tests, surveys, surveillance, or other data collection that will involve human subjects in the research are identified as research involving human subjects and submitted to the IRB for review. The investigator cannot begin research activities involving human subjects until receiving approval from the IRB. Changes in approved research during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

The Principal Investigator (PI) on a project submitted to the IRB for review has primary responsibility for protecting the rights and welfare of human research subjects and for complying with all applicable provisions of federal, state and local law and any requirements of the ORSIRB. PIs are encouraged to consult with the IRB early in the development of their proposals to ensure that (1) their studies are scientifically sound (worthy of involving human subjects), (2) the rights and welfare of subjects are fully considered in the study design, and (3) the study has a high likelihood of meeting the criteria for IRB approval.

Other institutions

Each participating institution may appoint a Human Subjects Coordinator (HSC) at their site or defer to the ORSIRB Administrator for guidance. The HSC or the ORSIRB Administrator is responsible for reviewing proposals submitted by the institution's PIs for completeness and compliance with the DOE Order 443.1b, 45 CFR 46 and 10 CFR 745.

Other Institutional Review Boards

The Central DOE IRB (CDOEIRB) serves as DOE's IRB of record for purposes of satisfying the human subjects' protection requirements of the DOE and U.S. Department of Health and Human Services (DHHS) for study protocols that involve employees of DOE or its contractors and/or are explicitly funded by, or conducted by, DOE or other agencies or institutions in the following areas:

- Human subjects research in which multiple DOE sites are engaged.
- The Former Worker Medical Screening Program (FWP), including the beryllium sensitization screening component.

The Central DOE IRB-Classified (CDOEIRB-C) serves as DOE's IRB of record for purposes of satisfying the human subjects' protection requirements of the DOE and U.S. Department of Health and Human Services (DHHS) for study protocols that include classified information. Classified projects are submitted directly to the CDOEIRB-C.

Regulatory agencies

Protecting the subjects of research is a shared responsibility and shall be operated and maintained in accordance with 10 CFR 745 and with 45 CFR 46, sub-parts B, C., D, and E, as well as DOE Order 443.1B.

ORSIRB STRUCTURE

Membership

Number of members

Following federal requirements the membership of the IRB shall:

- include one Chairperson and at least five members with varying background;
- include at least one scientist and one non-scientist;
- include at least one member who is not affiliated with the institutions other than serving on this board;
- be sufficiently qualified through the experience, expertise, and diversity of its members to permit complete and adequate review of research activities commonly conducted by these institutions; and
- be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.

When reviewing research involving a vulnerable population, such as children, prisoners, pregnant women, handicapped or mentally disabled persons. The IRB shall invite individuals with competence in these special areas to assist in the review of issues that may require expertise beyond or in addition to the expertise routinely available on the IRB. Such specialists shall not have voting rights.

Qualifications of members

IRB members must have knowledge of the specific scientific disciplines relevant to the research that it reviews. In addition to possessing the professional competence to review specific research activities, the IRB membership must be able to determine the acceptability of proposed research in terms of institutional commitments and policies, applicable laws and regulations, and standards of professional conduct and practice. The IRB must also possess knowledge of the local research context to fulfill its review responsibilities under federal regulations. If the appointed membership is not sufficiently knowledgeable about the scientific discipline, research context, or legal issues as related to a specific project, consultants may be used to supplement IRB review. If the IRB regularly reviews research involving identified vulnerable populations, the IRB will secure members experienced in working with such populations.

The ORSIRB membership will be assessed annually by the IRB administrator or designee 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 745.107 are fully satisfied.

Membership shall be sufficiently diverse (including consideration of race, gender, cultural background, and sensitivity to such issues as community attitudes) in order to evaluate categories of research presented to the ORSIRB. Therefore, membership must include:

- both men and women,
- multiple professions,
- scientific and nonscientific members, and
- not otherwise affiliated members.

Under the terms of the institution's FWA granted by OHRP, the ORSIRB (listed as the IRB of record) will be represented on the board by an institutional representative (one of whom must be a scientist), plus at least one member not affiliated with the institution and one non-scientist. The unaffiliated member and the non-scientist member may be the same person.

Scientist members are members whose training, background, and occupations would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline. Scientist members are recruited from among active or retired professionals and also from the community.

Non-scientist members are members whose training, background, and occupation would incline them to review research activities from a standpoint outside of any biomedical or behavioral scientific discipline. They may be recruited from among active or retired professionals and also from the community.

The unaffiliated representative may be a scientist or non-scientist, but at least one should be a non-scientist who represents the general perspective of participants; is sensitive to community attitudes in promoting respect of research participants regardless of race, gender and cultural background; and safeguards the rights and welfare of human subjects. To be eligible for

participation on the IRB, neither the member nor any member of his/her immediate family may otherwise have a direct affiliation (, employee, contractor, student in a fellowship, volunteer at the institution or business unrelated to the IRB) with the institution. The fact that an individual is a retiree or former employee of the institution does not necessarily constitute a direct affiliation.

Alternate members

Alternate members may be chosen by, among other qualifications, their ability to expand the expertise and/or diversity of the IRB.

Alternate members may attend all IRB meetings and participate in the discussion but are not counted towards quorum. They may not vote unless the regular member for whom they are appointed as an alternate is absent.

Alternate members may be assigned to replace a primary member in the event the primary member is unable to complete his or her duties.

MANAGEMENT OF THE IRB

Administrative Team

The Administrative Team consists of the Chair, Vice-Chair, IRB Administrator or any combination of these depending on the level of review required. It may also be necessary to add an IRB member with expertise in the study being reviewed. Duties of the administrative team vary and are described under the review procedures.

The Chair person

Selection and appointment

The Board shall nominate an active or former member to serve as its chair. The Board's nomination shall have the concurrence of a simple majority of members of the Board. The chair will be appointed by the IO of ORAU. The chair shall be qualified through experience and expertise, concerned about human rights and ethical issues, and familiar with regulations relevant to the use of human subjects in research. The chair must be an ORAU employee eligible to supervise the IRB Administrator.

Length of term/service

Once appointed the chair serves for indefinite renewable three year terms.

The immediate past chair is invited to attend meetings as a guest for a period of up to one year to provide expertise as needed to the new chair.

Duties

The chair is responsible for ensuring that the Board carries out its responsibilities. The chair also has the following responsibilities:

- Determines (along with the Administrative Team) the type of review required (Full Board or Expedited).
- Conducts expedited reviews or appoints expedited review subcommittees from the voting members of the Board.
- Acts as liaison with the IOs.
- Reports promptly to DOE/HQ and IOs any injuries to human subjects, any unanticipated problems involving risks to human subjects or others, any serious or continuing noncompliance with the requirements or determinations of the IRB, and any suspensions or terminations of IRB-approved research.
- Counts toward the quorum but does not vote unless there is a tie of the membership vote.
- Supervises the IRB Administrator.
- Determines when there is just cause for removal of a board member and makes recommendation to the IO to terminate as appropriate.

Removal

If at any time, issues related to a Chair's leadership, knowledge, or performance are identified, the IRB Administrator will discuss them with the IO of the institution. If appropriate, a plan for improvement may be implemented, including but not limited to, additional educational and/or mentoring activities. Failure to perform acceptably despite an improvement plan may result in being removed as IRB Chair as determined by the IO.

The Vice Chair

Selection and appointment

The Board shall nominate an active or former member to serve as the vice chair. The Board's nomination shall have the concurrence of a simple majority of members of the Board. The vice chair will be appointed by the IO of ORAU. The vice chair shall be qualified through experience and expertise, concerned about human rights and ethical issues, and familiar with regulations relevant to the use of human subjects in research.

Length of term/service

Once appointed the vice chair serves for indefinite renewable three year terms.

Duties

The IRB vice chair is responsible for ensuring that the Board carries out its responsibilities. The vice chair also have the following responsibilities:

- Acting as chair in the chair's absence, and

- Assisting with Board activities as requested by the chair

Removal

If, at any time, issues related to a vice chair's leadership, knowledge, or performance are identified, the IRB Administrator will discuss them with the IO of the institution and with the Chair. If appropriate, a plan for improvement may be implemented, including, but not limited to, additional educational and/or mentoring activities. Failure to perform acceptably despite an improvement plan may result in being removed as IRB vice chair as determined by the IO.

IRB Administrator

Selection and appointment

The IRB Administrator shall be qualified through experience and expertise, concerned about human rights and ethical issues, and familiar with regulations relevant to the use of human subjects in research. The IRB Administrator shall have or be able to obtain the Certified IRB Professional (CIP) certificate within two years of appointment. The position of the IRB Administrator is under the ORAU President's office, but reports to the IRB Chair.

Length of term/service

There are no term limits for the IRB Administrator.

Duties

The IRB Administrator is responsible for the day-to-day activities of the IRB and is the primary point of contact. The IRB Administrator also has the following duties:

- Acts as subject matter expert concerning the ORSIRB with DOE, other federal agencies, and the research community.
- Manages the administrative and record keeping requirements of the IRB.
- Ensure that research is conducted in accordance with all applicable regulations, policies, procedures, institutional requirements, and agreements.
- Ensures documentation of IRB activities is generated and maintained.
- Develops, along with the Chair, policies and standard operating procedures. Minor changes and updates are carried out as necessary. Major changes shall have the concurrence of a simple majority of members of the Board.
- Develops and facilitates education in compliance with federal agency and institutional requirements.
- Receives proposals submitted by each institution, reviews them for completeness and compliance, and forwards them to the IRB chair with an initial recommendation for the appropriate type of review.
- Arranges for teleconferences and/or in-person meetings including travel for Board members as required.
- Is encouraged to participates in the DOE Human Subjects Working Group (HSWG).

- Attends professional meetings and appropriate training as required to maintain certification as an IRB Administrator.
- Serves as the Secretary of Record for the Board in accordance with 10 CFR 745.115.
- Prepares and submits an annual report to the DOE Human Subjects Research Database (HSRD).
- Serves as a voting representative on the Board.
- Notifies DOE of any new human participants research projects involving:

    - An institution without an established IRB.
    - A foreign country.
    - The potential for significant controversy (, negative press or reaction from stakeholder or oversight groups).
    - Research subjects in a protected class.
    - The generation or use of classified or sensitive unclassified information.

Removal

If, at any time, issues related to the IRB Administrator's leadership, knowledge, or performance are identified, the Chair will discuss them with the IO of the institution. If appropriate, a plan for improvement may be implemented including, but not limited to, additional educational and/or mentoring activities. Failure to perform acceptably despite an improvement plan may result in being removed as IRB Administrator.

IRB members

Selection and appointment

Board members are responsible for nominating persons for membership to the Board New members will be officially notified of their appointment to the Board by the IRB chair. New members do not vote at their first Board meeting. A confidentiality statement and a statement to acknowledge any conflict of interest as it occurs will be signed at least annually. Only investigators who are not current board members are allowed to make a nomination.

Length of term/service

Board members serve renewable three-year terms. There is currently no limit on the number of terms a member may serve. Staggering terms for the members of the board is desirable for continuity.

Duties

- Members are expected to attend, actively participate in, and vote at meetings of the ORSIRB and to serve as reviewers of assigned applications.

Attendance requirements

- Members are expected to attend all meetings in person or via teleconference.

Removal

Just cause for removal from the board may include, but is not limited to, lack of minimum attendance (defined as three consecutive scheduled board meetings), misconduct, unresolved conflict of interest, failure to complete required training or failure to complete work as assigned or requested by the chair, vice chair, or administrator and shall be dealt with by the chair on a case by case basis.

Any issues related to members' performance will be discussed by the chair, IO, and the IRB administrator. A plan for improvement may be implemented. Failure to perform acceptably despite an improvement plan may result in being removed from membership on the IRB as determined by the IO.

Compensation of IRB members

An honorarium is given to unaffiliated IRB members and consultants when they are asked to do a primary or designated review, training, travel, or attending a meeting in person or by teleconference.

Liability coverage for IRB members

Liability insurance will be provided for members who otherwise do not have such insurance.

Use of consultants

If the board chair determines that consultants or experts are required to advise the board in its review of a protocol, such an expert or consultant will be recruited and will receive copies of the research protocol package. Their presence at the meeting as non-voting attendees or their written comments on the protocol package will be invited, whichever is more appropriate. Their opinions will be considered by the board in reaching its decision on the protocol.

An honorarium is given to consultants when they are asked to travel to attend a meeting or participate in a teleconference.

Secretarial/administrative support staff (duties)

Administrative support is available as needed. This includes preparation of meeting materials, assisting with travel, editing and proofing documents.

CONFLICT OF INTEREST

Researchers

In research, conflicts of interest (COIs) refers to situations in which financial or other personal considerations may (or may appear to) compromise a researcher's professional judgment in conducting or reporting research. Such conflicts may impart bias in collection, analysis, and interpretation of data, as well as the hiring of staff, procurement of materials, sharing of

results, choice of protocol, and the use of statistical methods. COIs are particularly important to consider in biomedical and behavioral research because of the potential impact on human health It is not possible to completely eradicate the potential for COIs because there are certain rewards that are inherent in the structure of the research enterprise. Such rewards may be completely unrelated to relationships with industry or private sponsorship. For example, positive research results per se may contribute to opportunities for publication, promotion, grant renewals, and so forth. In addition, positive results are often more gratifying and lead to greater personal satisfaction than negative outcomes. But kept in perspective, such incentives are not inherently bad and are indeed the motivating forces for diligent scientists. Such conflicts become detrimental when the potential rewards, financial or otherwise, cause deviation from absolute objectivity in the design, interpretation, and publication of research activities, or in other academic and professional decisions.

The mere appearance of a conflict may be just as serious and potentially damaging as an actual distortion of objectivity. Reports of conflicts based on appearances can undermine public trust in ways that may not be adequately restored even when mitigating facts of a situation are brought to light. Apparent conflicts should be evaluated and managed with the same rigor as known conflicts.

Some potentially problematic situations include:

Engaging in research when the PI or his or her immediate family has a financial, managerial, or ownership interest in the sponsoring company or in the product under evaluation

Accepting gratuities or special favors from research sponsors

Entering into a consultant arrangement with an organization or individual having an economic interest in related research

PIs are required to be familiar with their institutional policy on Conflicts of Interest, and should contact their Legal Counsel with questions or concerns regarding potential conflicts of interest with their research.

IRB Members

No IRB member may participate in the review of any protocol in which that member has a conflicting interest except to provide information requested by the IRB.

An IRB member is considered to have a conflict of interest when any of the following conditions have been met. The member:

- is also a member of the research team for the study under review;
- supervises any member of the research team or manages the program or organization conducting the study;
- has a financial interest in the research with a value that cannot be readily ascertained (this may include equity ownership, stock options, paid consultant fees, or patent, trademark, or licensing agreements); or

- has any relationship to the study, the sponsor, or any member of the research team that may be perceived as a conflict of interest.

Note: See the Conflict of Interest -- Researchers for a general discussion of the concerns related to this.

FUNCTIONS OF THE IRB

Conducting initial and continuing review

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 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.

A determination made by the Federal oversight office for human research, the HHS 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.

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

- anticipated benefits, if any, to subjects, and
- the importance of the knowledge that may reasonably be expected to result.
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(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.

(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. These requirements are incorporated in the ORSIRB review standards. For all initial protocol reviews, these standards must be addressed and recorded in the minutes.

IRB PROTOCOL REVIEW STANDARDS **Minimal regulatory requirements for IRB review, discussion and documentation in the meeting minutes**	
Regulatory review requirement	**Suggested questions for IRB discussion**
1. The proposed research design is scientifically sound & will not unnecessarily expose subjects to risk.	(a) Is the hypothesis clear? Is it clearly stated? (b) Is the study design appropriate to prove the hypothesis? (c) Will the research contribute to generalizable knowledge and is it worth exposing subjects to risk?
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.	(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?
3. Subject selection is equitable.	(a) Who is to be enrolled? Men? Women? Ethnic minorities? Children (rationale for inclusion/exclusion addressed)? Seriously-ill persons? Healthy volunteers? (b) Are these subjects appropriate for the protocol?
4. Additional safeguards required for subjects likely to be vulnerable to coercion or undue influence.	(a) Are appropriate protections in place for vulnerable subjects, e.g., pregnant women, fetuses, socially- or economically-disadvantaged, decisionally-impaired, prisoners or workers?

5. Informed consent is obtained from research subjects or their legally authorized representative(s).	(a) Does the informed consent document include the eight required elements? (b) Is the consent document understandable to subjects? (c) Who will obtain informed consent (PI, nurse, other?) & in what setting? (d) If appropriate, is there a children's assent? (e) Is the IRB requested to waive or alter any informed consent requirement?
6. Risks to subjects are minimized.	(a) Does the research design minimize risks to subjects? b) Would use of a data & safety monitoring board or other research oversight process enhance subject safety?

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.

CONSENT PROCESS

General Information

Delays in IRB approval commonly result from the submission of an inadequate consent form. The following guidelines are meant to assist you with the basic format of your consent form.

- **Fifth-grade reading level**—The primary goal of a consent form is to provide all required information about a study in language and format that is easily comprehensible, and presented at the most likely level of understanding of the subject population. For many studies, the consent form should be written at a fifth-grade reading level. Everyday vocabulary and simple sentence structure should be used throughout the form.
- **Lay language**—Unless the subjects are themselves medical professionals, scientific or technical terms should either be replaced with or defined in lay language. For example, "blood draw" is preferable to "venipuncture" and "x-ray" to "radiograph."
- **Non-legalistic language**—Legalistic sounding language such as "You hereby agree," "You certify that," "You, the undersigned, do acknowledge that," should not be used. Also, any phrases similar to the following should not be used: "You understand that," "You realize that," "You have been

told that," "It has been explained to me that." Not only do these phrases not ensure a subject's comprehension but they lend the appearance of a legal document to the consent form.

- **Consistent use of person**—The person in which the form is written should be used consistently throughout. The IRB recommends that the form be written in the second person of the subject, that is, "You have been asked to participate in a research study."
- **Page numbering and date**—As a record-keeping aid for the study subjects, the IRB members/staff, and the investigators, each page of the consent form should be numbered (preferably "1 of 2," "2 of 2"). In addition, the lower corner of each page of the consent form should include the date of this version of the consent form.
- **Correct spelling and grammar**—The entire form should be carefully proofread for correct spelling and grammar before it is submitted to the IRB for review.

As described in the Belmont Report, consent must be (1) informed, (2) understood, and (3) voluntary. These are the hallmarks of consent and provide respect for research subjects by honoring their autonomy. Informed consent is not just a form or a signature, but a process of information exchange that includes subject recruitment materials, verbal instructions, written materials, and question and answer sessions. The IRB and investigators share responsibility for ensuring that the informed consent process is adequate. Rather than an endpoint, the Consent Form should be the basis for a meaningful exchange between the investigator and the subject.

The Consent Form, or information sheet (an unsigned consent document), serves as a written summary of the exact information that is presented to a prospective subject. The investigator is responsible for ensuring that informed consent is obtained from each research subject before the subject participates in the research study. It also serves as a useful reference for both the subject and the investigator.

Obtaining Consent

Investigators should give careful consideration to the process whereby consent is obtained. This should include considerations of how, when, and by whom consent will be obtained. Considerations regarding any special subject population should be addressed, as well.

Children

Federal law defines children as "persons who have not attained the legal age for consent . . . under the applicable law of the jurisdiction." The legal age of consent varies from state to state. When a child is the subject of research, the IRB must determine whether adequate provisions are made for soliciting the assent of the child, as well as the permission of the child's parent or court-appointed guardian. Assent and permission are defined as follows:

Assent—a child's affirmative agreement to participate in research. Failure to object, absent affirmative agreement, should not be construed as assent. In general, children under the age of 7 are considered incapable of providing assent. Children between the ages of 7 and 12 are generally considered capable of providing assent, depending on the nature of the research and the individual child's maturity and psychological state. The assent process for children in this age group should be simplified so it is

comprehensible to the children. Children who are at least 13 years old can generally provide assent in a full and meaningful way.

The child's assent is required in all research where the subject has the capacity to comprehend aspects of the study. The assent process assures an element of understanding, cooperation, and a feeling of inclusion on the part of the child and also illustrates the investigator's respect for the rights and dignity of the child in the context of research. Investigators should remember that a child's mere refusal to object to participation in research should not be construed as assent. Out of respect for children as developing persons, they should be asked whether or not they wish to participate in the research, particularly if (1) the research does not involve interventions likely to benefit them and (2) the children can comprehend and appreciate what it means to be a volunteer for the benefit of others.

Parental permission—Current regulations tend to avoid the term "consent" when one person grants approval for another to participate in research. Parents or legal guardians therefore grant "permission" for children to participate in research (45 CFR 46.408). The "permission" form is, in essence, a consent document and should follow all applicable requirements for informed consent as outlined in this manual.

Whenever possible, the permission of both parents should be obtained; however, current federal regulations do not require permission from both parents in all research situations. In general, the risk to the child and the prospect of direct benefit for the child as a research subject determine whether single parental/guardian permission may be permitted. If the research involves no greater than minimal risk, permission of only one parent is sufficient [45 CFR 46.404]. If the research involves greater than minimal risk, consent of both parents must be obtained unless one parent is deceased, unknown, incompetent, not reasonably available, or when only one parent has the legal responsibility for the care and custody of the child [45 CFR 46.408(b)]. Investigators should obtain written permission from the parent/guardian prior to contacting a child for participation in research.

Non-English speaking subjects

If the study will include non-English speaking subjects, investigators should discuss the use of translators in the consent process and a copy of the translated Consent Form or information sheet should be submitted with the application.

Subjects unable to consent for themselves

For studies involving subjects who cannot give signed or even verbal consent for themselves (e.g., young children, mentally handicapped persons, unconscious patients) the IRB may waive this requirement if sufficient justification for use of the particular subject group is presented and if appropriate measures for obtaining consent from a legally authorized representative or a relative and/or subject advocate are followed. OHRP has reminded the IRBs of the mandate for obtaining legally effective informed consent prospectively from each research subject or the subject's legally authorized representative.

Alternatives

This section should discuss any alternatives to participation in the study. This can be a short statement, but it should make clear the possible choices (e.g., no participation, or some or all of the protocol treatment, but without participation in the study, etc.) that are available if the individual chooses not to participate in the study. If the study involves only normal, healthy volunteers, and thus the only alternative is to decline participation in the study.

Financial Considerations

Costs/Financial Considerations

When participation in the study may result in any costs whatsoever to the subjects, clear information must be provided in the consent form regarding these costs. It there are no costs to the subject, this should be clearly stated as well.

If any real or potential financial conflicts of interest have been identified regarding the research activity, that information, as it affects the subject's decision to participate, should be included.

Reimbursement/Payment

When referring to money that subjects will receive in return for participation in a study, either "reimbursement" or "payment" may be used. However, the term "compensation" should not be used because it is used on consent forms to designate compensation for injury. Investigators should avoid connotations of undue influence to participate or that the subject is being employed by the investigator. Rather, the sense should be that subjects will be reimbursed for their time, travel expenses, and the inconvenience of being a research subject.

This section should state the total dollar amount that the subject will be paid for participation in the study, and should give any other relevant information such as pro-rating if a subject does not complete the study, or bonus payment at the end of the study. If appropriate, a payment schedule should be included in this section. Subjects should not be required to complete the entire study in order to be reimbursed and bonus payments for study completion should be modest.

Subjects should be informed how payment will be made (e.g., in cash, by check) and when they will be paid (e.g., immediately after the interview, approximately six weeks after individual completion of the study). It is important that this information be clear and complete.

Payments for research participation in excess of $600 per calendar year are considered taxable income. If subjects will be paid more than $600, the Reimbursement section should explain that the institution will request the subject's Social Security number in order to report this income to the IRS.

If there will be no payment or reimbursement to subjects for study participation, this information should be stated in this section.

Questions

This section should provide contact information for the subject in case of questions about the study. The principal investigator's name and phone number must be included in this section as subjects often wish to contact the person who is supervising the project. Blank lines to be filled in later may be included for additional contact persons. If the person explaining the study and obtaining consent is not the principal investigator, the blank lines in this section may be filled in with that person's name, and telephone number, if different, at the time consent is obtained.

Informed Consent

PIs are required to provide informed consent documents that address all the elements of informed consent as prescribed in 10 CFR Part 745.116, and any additional elements required by DOE. Also, PIs are responsible for ensuring that legally effective informed consent documents comply with the following requirements:

- Be obtained using a consent form that has been reviewed and approved by the appropriate IRBs within the previous 12 months or less;
- Be obtained from the subject or the subject's legally authorized representative;
- Be in nontechnical language (ideally at an eighth-grade reading level) understandable to the subject or his/her representative;
- Clearly state that participation is voluntary and that the subject may withdraw at any time without penalty or loss of their rights;
- Be obtained under circumstances that offer the subject or the representative sufficient opportunity to consider whether the subject should or should not participate; and
- Not include exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights or language that releases or appears to release the PI, the sponsor, the institution or its agents from liability for negligence.

Elements of Informed Consent

Eight 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.

Additional elements of informed consent

According to 10 CFR 745.116(b), several additional pieces of information are required when, in the judgment of the ORSIRB, they are appropriate. These additional elements are:

- A statement that the particular treatment or procedure may involve risks to the subject (or the embryo or fetus if the subject is or may become pregnant) that are currently unforeseeable;
- Any anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- Any additional costs to the subject or their insurance carrier that may result from participation in the research;
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject; and
- The approximate number of subjects involved in the study.

Waiver or Alteration of Informed Consent

An IRB 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 IRB finds and documents in the project records and meeting minutes that the requirements of 10 CFR Part 745.116(d) are met:

- 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).

A waiver of informed consent may be requested in the case of records-based studies where the study participants will not be contacted and the primary risk from the study is loss of privacy. Procedures must be in place to protect the privacy of the data and to protect any PII. Requests for a waiver or alteration of informed consent must be initiated by the PI with the submission of the protocol, citing criteria from 10 CFR Part 745 and how the conditions of his/her protocol qualify under each criterion.

Documentation of Consent (10 CFR Part 745.117)

Except as otherwise waived or altered, informed consent will be documented by the use of the written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. The consent form may be either of the following:

- A written consent document that embodies the required elements of informed consent required in 10 CFR Part 745.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator will give either the subject or the representative adequate opportunity to read it before it is signed.
- A "short form" written consent document stating that the elements of consent have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there will be a witness to the oral presentation. The IRB will approve a written summary of the information being presented. The short form will be signed by the subject and/or the subject's legal representative and both will receive a copy of the summary information.

Subjects will be given a copy of the consent document for their keeping and future reference.

Waiver of Documentation of Informed Consent

An IRB may waive the requirement for the investigator to obtain a signed consent form [10 CFR Part 745.117(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.

INITIAL REVIEW PROCEDURE

The following procedure is depicted in the flowchart in Appendix A. The PI is encouraged to contact the IRB any time in this process.

The IRB can proceed with its review of a study before receiving confirmation that all necessary training has been completed.

The steps for initial review and approval are described in detail below. Procedures for amendment, continuing, and completion/termination reviews are discussed later in this section.

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 IRB 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, 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 IRB 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 IRB in the Electronic Management System (EMS).

For the IRB to conduct a review, the PI must submit their package in the EMS. 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

IRB Administrator Pre-Reviews Submitted Materials.

Upon receipt of the protocol package, the IRB Administrator:

- Reviews 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 (1) 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.
- Notifies the IRB chair, and the program manager at DOE and 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; or
    - the generation or use of classified or sensitive unclassified information, or
    - the potential to constitute Human Terrain Mapping (HTM).
- The email sent to the program managers is documented in the EMS.
- Assigns 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, IRB members receive the review materials two weeks prior to a scheduled meeting.

Full Board Review Procedure

IRB Full Board Reviews Proposed Study.

During the review, the IRB 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 the deliberations of the board. The chair or administrator also asks for and records the total vote of all eligible voting members.

The IRB evaluates the following requirements for approval to ensure that:

- Risks to subjects are minimized and reasonable in relation to anticipated benefits.
- Selection of subjects is equitable.
- Participation is voluntary. Informed consent will be sought from each subject if applicable and will be appropriately documented.
- Adequate provisions are made to protect subject privacy and confidentiality of data.

When any subjects are likely to be vulnerable to coercion or undue influence, additional safeguards are included to protect the rights and welfare of those vulnerable subjects .(See 45 CFR 46, Subparts B, C, and D)

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 and does not need future review by the Full Board.

IRB Approves, Defers, or Disapproves Proposed Study.

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

Approve as submitted - Study meets all requirements with no additional clarifications or changes.

Require modifications to secure approval - Study requires additional clarification 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.

In a Full Board vote, the IRB must indicate whether the response to required modifications can be reviewed and approved via the Administration Team consisting of the chair, vice chair, and administrator or must be returned for review and approval by the convened board. The date of the vote to approve shall be deemed the date of the Full Board convened meeting.

Defer - Protocol needs major work or lacks sufficient information for the IRB to complete its review.

When a study has too many issues to be approved, the IRB may defer the determination. The board must identify why the proposed work is not approvable in its current form and what issues need to be resolved before the IRB can proceed. Until the PI provides that information

and/or revises the submitted materials, the board can take no further action, and no activity may begin on the study. Deferring a study is rare, but when it occurs, the PI can either revise the submission package or abandon the project. There is no set time limit for the PI to respond, but one may be imposed on a case-by-case basis.

Disapprove - Protocol does not meet the minimum criteria required for approval.

The IRB may vote to disapprove an application to conduct human subjects research when it determines that the study design does not provide, and is unlikely to be modified to provide, adequate protection to subjects. Disapproval of an application usually follows several attempts by the PI, in conjunction with the efforts of the IRB, to modify the study design to afford protection to the subjects.

Only the convened IRB can disapprove a study, and this study-specific decision may not be modified by any other agency or entity. A principal investigator may submit a new study on the same research topic, without prejudice, if the IRB's reasons for disapproval in the first instance are fully addressed.

If the IRB disapproves a research activity, the PI will be notified of the decision in writing. The notification will include a statement of the reasons for disapproval and will provide instructions to the investigator regarding his/her right to respond to the IRB in person or in writing.

The IRB Administrator creates the applicable determination letter and issues it to the PI in the EMS. The IRB administrator must verify completion of all required training before the final approval letter for a non-exempt study letter can be issued.

Expedited Review Procedure

IRB Administrative Team Pre-Reviews Proposed Study

During the pre-review, the IRB 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 Administrative Team's discretion, an additional IRB member may be designated to assist in the review.

The IRB Administrative Team/Designated Reviewer evaluates the following requirements for approval to ensure that:

- Risks to subjects are minimized and reasonable in relation to anticipated benefits.
- Selection of subjects is equitable.
- Participation is voluntary. Informed consent will be sought from each subject if applicable and will be appropriately documented.
- Adequate provisions are made to protect subject privacy and confidentiality of data.

When any subjects are likely to be vulnerable to coercion or undue influence, additional safeguards are included to protect the rights and welfare of those vulnerable subjects. (See 45 CFR 46, Subparts B, C, and D)

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

IRB Approves or Defers Proposed Study.

Note: A study cannot be disapproved by the Expedited Review Process and would require Full Board review.

Approve as submitted - Study meets all requirements with no additional clarifications or changes.

Require modifications to secure approval - Study requires additional clarification 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.

In a Full Board vote, the IRB must indicate whether the response to required modifications can be reviewed and approved via the administration team or must be returned for review and approval by the convened boar The date of the vote to approve shall be deemed the date of the Full Board convened meeting.

Defer - Protocol needs major work or lacks sufficient information for the IRB to complete its review.

When a study has too many issues to be approved, the IRB may defer the determination. The board must identify why the proposed work is not approvable in its current form and what issues need to be resolved before the IRB can proceed. Until the PI provides that information and/or revises the submitted materials, the board can take no further action, and no activity may begin on the study. Deferring a study is rare, but when it occurs, the PI can either revise the submission package or abandon the project. There is no set time limit for the PI to respond, but one may be imposed on a case by case basis.

The IRB Administrator creates the applicable determination letter and issues it to the PI in the EMS. The IRB administrator must verify completion of all required training before the final approval letter for anon-exempt study letter can be issued.

Continuing Review Procedure

The following procedure is depicted in the flowchart in Appendix A. The PI is encouraged to contact the IRB any time in this process.

The IRB can proceed with its review of a study before receiving confirmation that all necessary training has been completed.

The steps for continuing review and approval are described in detail below. Procedures for initial, amendment/modification, and completion/termination reviews are discussed in other sections.

PI Submits Continuing Review Package to IRB in the EMS.

For the IRB to conduct a review, the PI must submit a continuing review package in the EMS. 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.
- 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.
- When applicable, any external IRB approval letters.

IRB Administrator Pre-Reviews Submitted Materials.

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.
- Assigns 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, 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.

Full Board Procedure for Continuing Review

IRB Full Board Reviews Continuing Review Package

During the review, the IRB 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 the deliberations of the board. The chair or administrator also asks for and records the total vote of all eligible voting members.

The IRB evaluates the following requirements for approval to ensure that:

- Risks to subjects are minimized and reasonable in relation to anticipated benefits.
- Selection of subjects is equitable.
- Participation is voluntary. Informed consent will be sought from each subject if applicable and will be appropriately documented.
- Adequate provisions are made to protect subject privacy and confidentiality of data.

When any subjects are likely to be vulnerable to coercion or undue influence, additional safeguards are included to protect the rights and welfare of those vulnerable subjects. (See 45 CFR 46, Subparts B, C, and D)

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.

IRB Approves, Defers, or Disapproves Study.

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

Approve as submitted - Study meets all requirements with no additional clarifications or changes.

Require modifications to secure approval – Study requires additional clarification 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.

In a Full Board vote, the IRB must indicate whether the response to required modifications can be reviewed and approved via the Administration Team consisting of the chair, vice-chair, and Administrator or must be returned for review and approval by the convened board. The date of the vote to approve shall be deemed the date of the Full Board convened meeting.

Defer - Protocol needs major work or lacks sufficient information for the IRB to complete its review.

When a study has too many issues to be approved, the IRB may defer the determination. The board must identify why the proposed work is not approvable in its current form and what issues need to be resolved before the IRB can proceed. Until the PI provides that information and/or revises the submitted materials, the board can take no further action, and no activity may begin on the study. Deferring a study is rare, but when it occurs, the PI can either revise the submission package or abandon the project. There is no set time limit for the PI to respond, but one may be imposed on a case by case basis.

Disapprove - Protocol does not meet the minimum criteria required for approval.

The IRB may vote to disapprove a continuing review application to conduct human subjects research when it determines that any changes to the study design do not provide, and is unlikely to be modified to provide, adequate protection to subjects. Disapproval of an application usually follows several attempts by the PI, in conjunction with the efforts of the IRB, to modify revised study design to afford protection to the subjects.

Only the convened IRB can disapprove a study, and this study-specific decision may not be modified by any other agency or entity.

If the IRB disapproves a research activity, the PI will be notified of the decision in writing. The notification will include a statement of the reasons for disapproval and will provide instructions to the investigator regarding his/her right to respond to the IRB in person or in writing.

The IRB administrator creates the applicable determination letter and issues it to the PI in the EMS. The IRB administrator must verify completion of all required training before the final approval letter for a non-exempt study letter can be issued. Access to these determinations are available to the IO in the EMS.

Expedited Procedure for Continuing Review

IRB Administrative Team Assigns a Designated Reviewer

During the pre-review, the IRB 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 IRB Administrative Team/Designated Reviewer evaluates the following requirements for approval to ensure that:

- Risks to subjects are minimized and reasonable in relation to anticipated benefits.
- Selection of subjects is equitable.
- Participation is voluntary. Informed consent will be sought from each subject if applicable and will be appropriately documented.
- Adequate provisions are made to protect subject privacy and confidentiality of data.

When any subjects are likely to be vulnerable to coercion or undue influence, additional safeguards are included to protect the rights and welfare of those vulnerable subjects. (See 45 CFR 46, Subparts B, C, and D).

The Designated Reviewer Approves or Defers Proposed Package

The designated reviewer completes the non-committee review and determines the expedited or exempt category, or determines that Full Board review is required. The package may be:

Note: A continuing review package cannot be disapproved by the Expedited Review Process and requires Full Board review.

Approve as submitted - Study meets all requirements with no additional clarifications or changes.

Require modifications to secure approval - Study requires additional clarification 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.

In a Full Board vote, the IRB must indicate whether the response to required modifications can be reviewed and approved via the Administration Team or must be returned for review and approval by the convened board. The date of the vote to approve shall be deemed the date of the Full Board convened meeting.

Defer - Protocol needs major work or lacks sufficient information for the IRB to complete its review.

When a study has too many issues to be approved, the IRB may defer the determination. The board must identify why the proposed work is not approvable in its current form and what issues need to be resolved before the IRB can proceed. Until the PI provides that information and/or revises the submitted materials, the board can take no further action, and no activity may begin on the study. Deferring a study is rare, but when it occurs, the PI can either revise the submission package or abandon the project. There is no set time limit for the PI to respond, but one may be imposed on a case-by-case basis.

The IRB Administrator creates the applicable determination letter and issues it to the PI in the EMS. The IRB administrator must verify completion of all required training before the final approval letter for a non-exempt study letter can be issued. Access to these determinations are available to the IO in the EMS.

Modification Review Procedure

Modifications can be major or minor.

Major modification: A major modification is one which makes a substantial alteration in (1) the level of risks to subjects, (2) the research design or methodology, (3) inclusion of vulnerable population, (4) addition of procedures that would not otherwise be eligible for expedited review.

Minor modification: No substantial alteration to (1) the level of risk to subjects; (2) the research design or methodology; (3) the qualifications of the research team; (4) the facilities available to support safe conduct of the research. Examples include changes in the research team, minor wording changes in the consent form(s), recruiting materials or measures, minor changes in compensation, time of participation, subject recruitment, or change in funding status. Example: New funding source/sponsor or increase/decrease in funding

PI Submits Modification Package to IRB in the EMS.

For the IRB to conduct a review, the PI must submit a modification package in the EMS. The 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.

The IRB Administrative Team Pre-Reviews Proposed Study Package

During the pre-review, the IRB Administrative Team documents any issues identified and 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. At the Administrative Team's discretion, an additional IRB member may be designated to assist in the review.

The IRB Administrative Team/Designated Reviewer evaluates the following requirements for approval to ensure that:

- Risks to subjects remain minimized and reasonable in relation to anticipated benefits.
- Selection of subjects continues to be equitable.
- Provisions are still adequate to protect subject privacy and confidentiality of data.

When any subjects are likely to be vulnerable to coercion or undue influence, additional safeguards continue to be included to protect the rights and welfare of those vulnerable subjects.(See 45 CFR 46, Subparts B, C, and D).

Depending on the determination made by the IRB Administrative Team/Designated Reviewer, the modification is either assigned to a full board review or reviewed by the Expedited procedure

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 for review.

Expedited

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

The IRB Administrator creates the applicable determination letter and issues it to the PI in the EMS. The IRB administrator must verify completion of all required training before the final approval letter for a non-exempt study letter can be issued. Access to these determinations are available to the IO in the EMS.

Research Eligible for Exempt Review (Administrative Only)

Some research involving human subjects, their bodily materials, or personal data does not require IRB review and approval, but does require administrative review by the ORSIRB Office. In order to fulfill federal requirements for the proper review of these activities, the ORSIRB has assured the DHHS that all research activities involving human subjects or their identifiable, private information, whether funded or not, will be reviewed to determine whether or not further review by the ORSIRB is appropriate. If the ORSIRB Office determines that the research

is exempt from federal requirements governing human subjects research, an Exemption determination letter in the EMS will be issued.

Research Exempt from 45 CFR 46

45 CFR 46 identifies several categories of human subjects research activities that may not require review by the IRB. 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, in vitro fertilization, prisoners, the mentally disabled, or other "vulnerable" populations. The exemption categories follow.

Existing Data, Documents, Records, or Specimens

Research in which the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens is considered "existing" if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or through identifiers linked to the subjects. Note: Research involving human ova (fertilized or not) is not exempt

Tests, Surveys, Interviews, or Observation of Public Behavior

There are three types of research that fall into this category:

- Research involving the use of educational tests (e.g., cognitive, diagnostic, aptitude, and achievement tests), survey procedures, interview procedures, or observation of public behavior, unless: (1) information obtained is recorded in such a manner that human subjects can be identified directly or through identifiers linked to the subjects; and (2) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. The IRB Office is required to review copies of the informed consent form and proposed questionnaires or survey instrument(s) prior to approval and implementation. Survey or interview procedures involving children do not qualify for this exemption.
- Research involving the use of educational tests (e.g., cognitive, diagnostic, aptitude, and achievement tests), survey procedures, interview procedures, or observation of public behavior that is not exempt under if (1) the human subjects are elected or appointed public officials or candidates for public office or (2) federal statute(s) require(s), without exception, that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
- Research conducted in established or commonly accepted educational settings that involve normal educational practices, such as (1) research on regular and special education instructional strategies or (2) research on the effectiveness of or the

comparison among instructional techniques, curricula, or classroom management methods.

Public Service or Benefit Programs

This category includes research and demonstration projects that are conducted by or are subject to the approval of department or agency heads, and that are designed to study, evaluate, or otherwise examine (1) public benefit or service programs, (2) procedures for obtaining benefits or services under those programs, (3) possible changes in or alternatives to those programs or procedures, or (4) possible changes in methods or levels of payment for benefits or services under those programs.

Taste and Food Quality Evaluations at the DHHS

This category includes taste and food quality evaluation and consumer acceptance studies if (1) wholesome foods without additives are consumed or (2) a food is consumed that contains either (a) a food ingredient at or below the level and for a use found to be safe or (b) an agricultural chemical or environmental contaminant at or below the level found to be safe by the Food and Drug Administration (FDA) or one approved by the Environmental Protection Agency (EPA) or the Food Safety and Inspection Service of the U.S. Department of Agriculture (USDA).

"Engaged in Research" Activities

Based on federal guidance from the OHRP, the ORSIRB has determined that DOE employees are considered not to be "engaged" in human subjects research if:

- Their involvement is limited to performing commercial services for outside organizations or institutions (or performing other genuinely non-collaborative services meriting neither professional recognition nor publication privileges), and
- They adhere to commonly recognized professional standards for maintaining privacy and confidentiality (e.g., an appropriately qualified laboratory performs analyses of blood samples for investigators solely on a commercial basis).

Additional Considerations

Although research in the above mentioned categories may not require review by the IRB, there are additional concerns that the ORSIRB Office will consider during the administrative review, and which may impact on the final determination. Receiving a Notice of Exemption does not mean that the investigator is exempted from addressing these concerns.

Anonymous Data

Data are considered to be anonymous when there is no possible way to identify the participants from the data collected. Data are not anonymous if anyone, or any procedure such as accessing a computer database, will identify the subject. In most instances, the omission of specific identifiers, such as name, social security number, or patient number, is sufficient to qualify a study as anonymous. Sometimes an investigator may preserve a subject's anonymity while still retaining data on individual characteristics such as age, gender, ethnic origin, occupation, or diagnosis. Anonymity is possible only when studying large samples or populations. When the number of potential participants is small and/or the research setting is identified, anonymity can be threatened or compromised even when identifiers have been removed from the data.

Archived pathology or diagnostic specimens that are considered residual biological material and destined to be destroyed can be used in research. They are considered exempt from IRB review if there are no patient identifiers linked to the specimen and if the data is not intended to be used in the diagnosis or treatment of a patient. If either of these conditions apply, then consent of the research subject is required and the study will require IRB review.

Use or collection of anonymous human biological specimens for research efforts focused on understanding, diagnosing, and treating genetic diseases will require review by the IRB. There are additional ethical concerns for genetic research (e.g., the potential for discrimination with regards to employment or insurability) that may not apply for other types of research with biological specimens. Please contact the IRB Office for additional information.

Existing Data

The term "existing" refers to the time period that the data or material was obtained. Federal guidance clearly states that the term "existing" refers to material or tissue that was "archived" or "on the shelf" prior to IRB review of the research. If the data/specimens are collected after the submission of the IRB application, then the data 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.

Research Involving Surveys or Questionnaires

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.

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.

Use of Consent Forms

A Notice of Exemption does not necessarily exempt investigators from the requirement of obtaining written informed consent from subjects. Most research involving surveys, questionnaires, or otherwise interacting with subjects will require the use of a consent form. For studies where there are no subject identifiers (i.e., when anonymous data is collected), an information sheet or cover sheet is usually required.

REQUIRED TRAINING

Member Training

Orientation

The IRB Administrator meets with each new board member to describe the operations of the IRB and what is expected of IRB members. During this orientation, the Administrator notes how the new member can access the IRB website, which includes links to this IRB Procedures Manual, DOE 443.1B, and the Belmont Report. All members must complete Collaborative IRB Training Initiative (CITI). Successful completion requires 80% accuracy. All members must complete EMS training.

Continuing education

Additional training is provided at each meeting and through regular email from the IRB Administrator (articles, press releases, and newsletters on current issues).

Time is allocated as needed on the meeting agenda to address current issues and pending changes in regulations. The IRB Administrator and Chair also use this time to disseminate information gleaned from national meetings and conferences they attended throughout the year.

Members are required to successfully complete CITI refresher training every three years for active members.

Reference material (IRB library)

The IRB Administrator maintains a library of reference material that may be checked out at any time by IRB members.

Research Team

For all studies that require Expedited or Full board review, Collaborative IRB Training Initiative (CITI) is mandatory for the PI and every member of the research team who interacts directly with human subjects or their personally identifiable information (PII). Depending upon the nature of the research either "biomedical research" or "social and behavioral research" modules may be chosen. Upon successful completion of this online course, CITI will automatically send a completion certificate to both the trainee and the IRB Administrator.

Administrative staff and Institutional Official

Collaborative IRB Training Initiative (CITI) is mandatory. The required modules are specified under "IRB members and Administrative staff" in CITI.

Refresher training

The applicable refresher training is required every 3 years. The EMS will send out notification starting 90 days before expiration.

For instructions, contact the IRB Administrator at ORSIRB@orau.org. The link to the training is www.citiprogram.or

SPECIAL RESEARCH ISSUES

Some human subjects research (HSR) involves issues that require additional attention. This section describes what those issues are, why additional concerns attach to those issues, and what to do if your research involves one of these.

Human Terrain Mapping (HTM)

What is HTM?

DOE defines HTM this way:

"Research and data gathering activities that are 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."

Who determines whether a study involves HTM?

The following procedure is used to determine whether proposed work constitutes HTM.

HTM Determination Procedure

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 funding program (SPP, LDRD, et), or from other sources. The IRB Administrator discusses the project with the PI and others as necessary to gather sufficient information to help determine if it qualifies as HTM.

The IRB Administrator emails a description of the study (typically the SPP or LDRD proposal) to DOE Human Subjects Protection (HSP) Program Manager(s).

DOE Human Subjects Protection (HSP) Program Manager(s). and the IRB Administrator, along with the PI and/or sponsor as needed, discuss whether the proposed work constitutes HTM. The DOE HSP Program Manager(s) makes the final decision and notifies the IRB Chair and/or Administrator.

The IRB Chair and/or Administrator notifies the PI, the funding source and SSP the DOE HSP Program Manager(s) decision.

If HTM, all requirements listed below apply.

If not HTM, the review / approval process proceeds as any other HSR.

HTM-specific requirements

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 Human Subject Protection (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 principal investigator (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 recognized DOE site IRB is the only entity authorized to determine whether the HTM data received by the PI after project initiation meets DOE criteria for de-identification. If the DOE site does not manage or operate its IRB, then the Central DOE IRB shall be the responsible IRB.

All Strategic Partnership Projects (SPP) Program-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.

Collaborative Projects

When conducting cooperative research projects that involve the site one or more other institutions, the site and the other institution(s) shall each be responsible for safeguarding the rights and welfare of human subjects. The site may enter into a joint review arrangement, may rely upon the review of the cooperating institution's qualified Institutional Review Board (IRB), or may make similar arrangements to avoid duplication of effort in accordance with federal regulations.

Classified Research

Federal law prohibits the use of Expedited review for classified studies. Accordingly, unless the work qualifies as Exempt, it must be reviewed by the full board at a convened meeting. Such reviews must be conducted in a secure environment, and each member present must have the appropriate security clearance. A majority of IRB members, including at least one non-scientist, must be present at this secure review. However, if the classified aspect(s) can be separated out and the resulting unclassified description retains sufficient information for the IRB to understand the study and render a determination, then it may be possible to review only the unclassified portions of the study. It is essential that the unclassified description presented to the IRB truly convey the entire study without omitting any critical elements. Accordingly, to determine whether the IRB can proceed with a review of the unclassified version, the IRB Chair

and/or the IRB Administrator must have full knowledge of the entire study, including the classified portions.

Current guidance for IRB review of classified studies is contained in Best Practices for Reviewing Classified Human Subjects Research (HSR) at DOE sites.

Note: DoD funded classified HSR that is not exempt must be approved by the Secretary of Defense [DoD Instruction 3216.02.13a] Other sponsor-specific requirements may be in effect.

International Projects

Research on human subjects must adequately protect the rights and welfare of the subjects regardless of where that research is conducted. All human subjects research that would be subject to US federal regulations if conducted wholly within the United States, must comply with federal regulations, DOE directives, and ORSIRB policies.

In addition to IRB review and approval, HSR conducted outside the US may involve international and country-specific requirements, including review by the appropriate local equivalent of an IRB. The federal 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

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 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,

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

Medical Devices and Research Regulated by the FDA

Most ORAU/ORNL research is not subject to Food and Drug Administration (FDA) regulations. However, some work, including research involving prosthetics and enhancing human abilities can fall under the medical devices section of FDA. See the FDA Medical Device website for current information or contact the IRB Administrator.

Vulnerable Populations

Pregnant Women, Human Fetuses, or Neonates

Research involving pregnant women, human fetuses, or neonates that is not otherwise approvable under Subpart B may be approved after special review by DHHS (45 CFR 46.207). DHHS will conduct or fund research that the IRB does not believe meets the requirements of 45 CFR 46.204 or 45 CFR 46.205 only if:

- the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates; and
- the Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines (, science, medicine, ethics, law) and following an opportunity for public review and comment.

Prisoners

DHHS regulations at 45 CFR 46, Subpart C, detail special additional protections for research involving prisoners who, because of their incarceration, may have a limited ability to make truly voluntary and uncoerced decisions about whether or not to participate as subjects in research

A prisoner is defined as any individual involuntarily confined or detained in a penal institution

To review research involving prisoners covered by the DHHS regulations, IRBs must:

- have a majority of its members not otherwise associated with the prison (45 CFR 46.304(a); and
- include a prisoner or a prisoner representative with appropriate background and experience to serve in this capacity, unless the research has already been reviewed by an IRB that included a prisoner or prisoner representative (45 CFR 46.304(b)).

Children

DHHS regulations at 45 CFR part 46, Subpart D, and FDA regulations at 21 CFR Part 50, Subpart D, require that special protections be provided for research involving children. Under the regulations, children are defined as persons who have not attained the "legal age" (in their jurisdiction) for consent to treatments or procedures that may be involved in the research, under applicable law of the jurisdiction in which the research will be conducted

Note: Additional protections for vulnerable populations are described in 45 CFR 46, Subparts B, C, and D.

Internet Research

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 IRBs/HSPP. The applicable DOE site IRB is the only entity authorized to approve the information to be used. If the DOE site does not

CO-WORKERS AS SUBJECTS

Co-workers may not appear very susceptible to undue influence. Yet, all personnel (employees, contractors, and students) are vulnerable to perceived, even if unintended, pressures to appear cooperative and supportive of projects conducted by their supervisor and co-workers. Additionally, when the subject pool consists entirely of people who are or maybe familiar with the study, the validity of the data collected 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 their ready availability or malleability. Accordingly, if research plans include recruitment of fellow workers from within the PI's group, justification will need to be include 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.

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 ORSIRB 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.

Use of Cell Lines and Datasets

Cell Lines

- Research using de-identified immortalized cell lines that are obtained from commercial or governmental sources is not considered human subject research, is not governed by 10 CFR 745 or 21 CFR 50&56, and review by the ORSIRB is not required.
- Research using an immortalized cell line that is not commercially or governmentally available must be submitted to the ORSIRB to determine whether or not it is exempt.
- Research to establish a cell line requires ORSIRB review and approval.
- Use of cell lines for potential commercial purposes is permissible in some circumstances with ORSIRB approval.

Datasets

- Research using de-identified datasets that are obtained from a commercial or governmental source is not considered human subject research, is not governed by 10 CFR 745 or 21 CFR 50&56, and review by the ORSIRB is not required.
- All other research involving datasets, whether identified or de-identified, requires ORSIRB review.

OTHER CONSIDERATIONS

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 web site or contact the ORSIRB Administrator.

The HIPAA Privacy Rule protects the confidentiality of personally identifiable data arising 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 approval by an Institutional Review Board (IRB) or Privacy Board.

The ORSIRB will review and approve access to protected health information (PHI) only if the PHI is held at the investigator's institution. When an ORSIRB investigator is a collaborator on a study that accesses PHI at a medical center or other covered entity, the IRB at that institution is responsible for reviewing and approving access. Although the allowable means of accessing PHI are spelled out in the HIPAA regulations, the investigator should check with the institution holding the PHI regarding their specific HIPAA policies and procedures.

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.

Deception or Withholding Information

The intent of informed consent is comprehensive, honest, and understandable disclosure of all elements of the subject's participation in research. However, some research necessitates that PIs withhold information about the real purpose of the study or intentionally give subjects false information about some aspect of the research in order to prevent subject bias. As a result, subjects cannot give fully informed consent prospectively.

Generally, minor deception, such as withholding the real purpose of a minimal risk study is acceptable, provided that (a) the research involves no more than minimal risk and (b) subjects are debriefed afterward.

The PI must justify the reasons for deceiving or withholding information from subjects, and provide a debriefing script or copy of the information that subjects will receive after participation. The debriefing should occur as early as feasible, preferably at the conclusion of subject's participation, but no later than at the conclusion of the data collection. After debriefing, subjects should be allowed to withdraw their data.

PRIVACY AND CONFIDENTIALITY

Privacy refers to a person's interest in controlling other's access to data about him/herself. Confidentiality is an extension of the concept of privacy; it refers to data (some record about the person, such as notes or a videotape of the person) and to how data are to be handled in keeping with the subjects' interest in controlling the access of others to information about themselves. Ideally, confidentiality is handled in an informed consent agreement between investigator and subject; the agreement states what may be done with private information that the subject conveys to the investigator. The terms of the confidentiality agreement need to be tailored to the particular situation.

Investigators are required to maintain and protect the privacy and the confidentiality of all personally identifiable information of all human subjects participating in research, except as may be required by law or released with the written permission of the subject. Subjects have the right to be protected against invasion of their privacy, and to expect that their personal dignity will be maintained and the confidentiality of their private information will be preserved. The more sensitive the research material, the greater the care required in obtaining, handling, and storing data.

Information through which subjects may be identified include their names, employee numbers, hospital ID numbers, social security numbers, driver's license numbers, home addresses, photographs, videotapes, and the like. Individuals also may be identified by description, for example, as the personnel manager in a particular company, the sixth grade teacher in a certain school, or the pediatric nurse at a local hospital. If information or data to be collected may be traced back to individual subjects, safeguards should be provided to ensure confidentiality.

Investigators will be asked by the IRB to describe how the data and links to subjects will be stored and maintained. They should also consider whether or not they will (1) provide information about subjects to others not involved in the research and (2) provide information they have learned about the subjects to the subject. Finally, investigators should consider to what extent a breach of confidentiality or invasion of privacy would constitute harm. If harm is a possibility, investigators must provide adequate provisions to protect participants from those harms and inform subjects of the possible harm.

Guidelines for protecting confidentiality

• Limit recording of personal information to that which is essential to the research.

• Store personally identifiable data securely and limit access to the principal investigator and authorized staff.

• Code data as early in the research as possible, and when appropriate, develop a plan for the ultimate disposition or destruction of the code linking the data to individual subjects.

• Apply for federal Certificates of Confidentiality in all situations for which certificates are reasonable and available. (Contact the IRB Office for further information.)

• Do not disclose personally identifiable data to anyone other than the research team without the written consent of the subjects or their legal representative. (Exceptions may be made in case of emergency need for intervention or as required by regulatory agencies).

REPORTING REQUIREMENTS

Once the study begins, the PI must keep in touch with the IRB at regular intervals. All non-exempt research approved by the IRB must be re-reviewed at least once a year during a continuing review. Each fall, the IRB is required to report to DOE on all research it reviewed during the previous fiscal year. Additionally, when a study is completed, an Application for Continuing Review or Closure Request form must be filled out and submitted in the EMS that includes a summary report describing the results of the study.

Several situations and events must be reported within very specific timeframes. To help researchers understand which, if any, of these situations or events might apply to their circumstances, the Reporting Table in Appendix D defines each event type and provides examples of each. The Table also stipulates who must report what to whom and when.

Situations that indicate “immediate” and “within 24-hours” reporting, must be submitted in the EMS.

Determining which studies require review more often than annually

If, during the initial review of a research protocol, the IRB determines that a study involves only minimal risk*, annual review is usually sufficient. However, if the study involves more than minimal risk, or other factors the following procedure is invoked.

The IRB determines aspects of potential risks:

- nature (physical, psychological, social, economic);
- severity (moderate, high, severe);
- probability (low, moderate, high); and
- duration (temporary, permanent).

The IRB determines whether the following are factors in the study:

- health and vulnerability of subjects involved,
- previously reported adverse events in similar studies,
- researcher and research team experience with the proposed work, or
- PI history (causes for concern on previous research).

The IRB assigns a review frequency (Appendix B) that is appropriate to the risk. For example, if a study involves no more than minimal risk, but the PI has had trouble managing past studies, requiring a progress report or continuing review at six months may be appropriate. For another PI conducting the same study this may not be warranted. The reason for this determination is documented in the EMS and the PI is notified of the frequency of review required.

- The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

As an alternative (or in addition) to increased review frequency, the IRB may elect to implement the following measures:

- Have an IRB member monitor the consent process.
- Have an IRB member or third party observe research activities.
- Implement stronger controls to protect privacy and confidentiality.
- Interview subjects after participation.

Determining which studies need verification from sources other than the investigator that no material changes have occurred since previous IRB approval.

The IRB will seek verification from sources other than the PI to ensure that no material changes have occurred since previous IRB review when:

- The IRB doubts the veracity of the information provided by the PI.
- The information provided by the PI is inconsistent with other information and the inconsistency cannot be resolved through discussion with the PI.
- The PI has been found to be in serious or continuing noncompliance on other projects.
- The IRB determines that verification from sources other than the PI is prudent.

The IRB uses the criteria in Appendix C to determine when such verification is necessary. Such verification may include:

- Conducting audits or inquiries to collect information,
- Observing or having a designee observe the informed consent process and conduct of the research.

ADVERSE EVENTS AND UN-ANTICIPATED PROBLEMS

An adverse event is any undesirable incident, experience, or outcome associated with a subject's participation in the research, whether or not considered related to the research. Adverse events must be reported to the IRB verbally and submitted in the EMS within five work days.

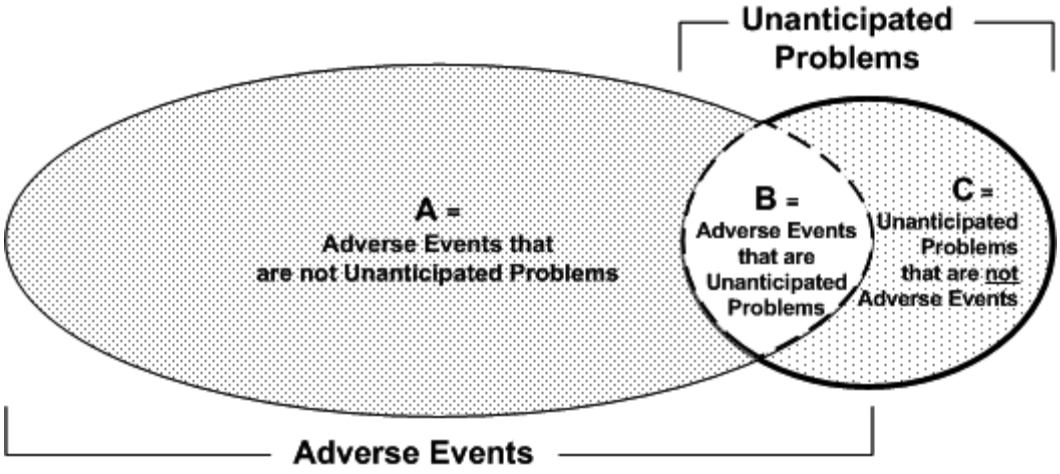
A serious adverse event is one that meets any of the following criteria:

- results in death
- is life-threatening
- results in subject hospitalization
- results in persistent or significant disability/incapacity or other harm
- results in congenital anomaly/birth defect, or
- requires medical or surgical intervention to prevent one of the above outcomes

Serious adverse events must be reported immediately. When an adverse event occurs, the PI must evaluate the adverse event to determine whether it also constitutes an unanticipated problem.

The Venn diagram below** summarizes the general relationship between adverse events and unanticipated problems:

[from OHRP Guidance on Unanticipated Problems and Adverse Events January 15, 2007]



Under 45 CFR part 46: Do not report A, Do report (B+C)

The diagram illustrates three key points:

The vast majority of adverse events occurring in human subjects are not unanticipated problems (area A).

A small proportion of adverse events are unanticipated problems (area B).

Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events (area C).

To determine whether an adverse event constitutes an unanticipated problem, ask the following questions:

- Is the adverse event unexpected in nature, severity or frequency?
- Is the adverse event related or possibly related to participation in the research?
- Does the adverse event suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized? Note: if the adverse event is serious, the answer is always "Yes."

If the answer to all three questions is yes, then the adverse event is an unanticipated problem and must be reported as such. If the answer to any question is no, the adverse event is not an unanticipated problem. If unsure, the IRB Administrator should be contacted.

In reviewing an adverse event, the IRB will consider whether it affects the risk/benefit ratio to ensure adequate protection of the welfare of subjects. In consultation with the PI, and if its investigation warrants, the IRB may:

- Reconsider approval of the study.

- Require the researcher to modify the protocol to minimize risks to subjects.
- Revise protocol to reflect the risks to subjects.
- Require subjects be re-consented or notified of additional information.
- Require no additional action on the part of the PI.

Noncompliance/Violations/Complaints

When the actual activities being performed in a study vary from what was reviewed and approved by the ORSIRB, the study is not in compliance with that approval. Reports of such a variance may come from a variety of sources: research subjects, ORSIRB members, research staff, or even people not connected with the research.

Anyone who suspects a problem with a study involving human subjects should report it to the IRB. All reports of non-compliance, alleged violations of human subject regulations, and complaints from research subjects will be investigated by the IRB. Allegations that are substantiated will be forwarded to the ORSIRB Chair for appropriate action.

The ORSIRB Chair will promptly report the following to the institutional official and to DOE:

- any unanticipated injuries or problems involving risks to subjects or others,
- any serious or continuing noncompliance with the regulations or requirements of the ORSIRB, and
- any suspension or termination of ORSIRB approval for research.

Deviation from Approved Protocol

Any individual noting a deviation from an approved protocol should report the deviation or concern to the ORSIRB. The ORSIRB will then review the protocol and 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.

The ORSIRB will determine whether the violation is serious (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 ORSIRB will also determine whether further corrective action is warranted:

- If the protocol violation is deemed serious, the ORSIRB will suspend the study.
- If the protocol violation is deemed non-serious, a memo will be sent from the ORSIRB Chair to the PI's manager.
- If the ORSIRB finds a pattern of protocol violations by a particular PI with no evidence of effective corrective action by the PI's manager, the ORSIRB will suspend all protocols for which the individual is the PI and request the PI's manager to conduct a root cause investigation.
- All findings and conclusion of the ORSIRB will be documented in the protocol file.

SUSPENSION/TERMINATION

The IRB has both the authority and the responsibility to suspend or terminate any research involving human subjects that is not being conducted in accordance with the IRB requirements or that has been associated with any unexpected serious harm to subjects. Any such suspension or termination of approval must be reported promptly to the PI and shall include a statement of the reasons for the suspension. The IRB Chair must also notify the appropriate Institutional Official, the PI's management, DOE, and, if applicable, OHRP.

If a PI fails to submit a completed Application for Continuing Review or Closure form prior to the IRB Approval expiration date, the IRB Administrator will contact the PI and his/her manager to inform them that the PI is no longer authorized to continue the study. All work, including data analysis, must stop on the expiration date, unless IRB approval has been renewed.

Note: The IRB makes every effort to avoid suspension of an otherwise active protocol and to prevent studies from being conducted beyond the approval period.

A suspended study may be re-opened after the problem triggering the suspension has been resolve A terminated study may not be reopened.

IRB Suspension/Termination Procedure

The IRB Chair notifies the IRB Administrator, the PI, and the PI's manager of their decision.

The IRB Administrator:

- Prepares a letter to DOE and OHRP (if applicable) to report the action.
- Sends form FDA 3500(6/83) to the FDA, if applicable, to report the action.
- Notifies the sponsor of the research of the action.

The full IRB reviews the suspension or termination as soon as possible.

OPERATIONS OF THE IRB

Scheduling of meetings

One or two convened meetings of the Board either in person or by teleconference shall occur at least within a 12-month period. Meetings may be held more frequently as necessary to ensure that the Board meets its responsibilities in accordance with 10 CFR 745. A PI may request, or be requested, to attend a meeting in person or by teleconference to discuss his/her protocol; however, no PI may be present during deliberations or voting on his/her proposal.

The IRB Administrator prepares a preliminary agenda for each meeting. A tentative agenda and copies of each project assigned to the meeting will be available in the EMS at least one week prior to the meeting allowing adequate time for members to review studies before the meeting and for any follow-up they may be expected to do with the researcher before the meeting. Paper copies will be distributed on a case-by-case basis.

Primary Reviewers

When the IRB uses the Primary Reviewer System, the primary reviewer(s) should do an in-depth review of all pertinent documentation (application, protocol, informed consent, advertisements, recruitment materials, questionnaires, survey instruments, and any other relevant material). All other IRB members should receive and review a protocol summary (of sufficient detail to make the determinations required under DHHS regulations at 10 CFR 745.111), the proposed informed consent document, and any advertising material. A reviewer document is available in the EMS.

Quorum required to transact business

A quorum is defined as more than half the number of regular or alternate voting members of the IRB and must include at least one non-scientist. At least one unaffiliated member who represents the general perspective of subjects should be present at the majority of meetings in a given year. Before the start of each meeting the IRB Chair and IRB Administrator determine and document that quorum has been met. A quorum (including the non-scientist) must be present for each formal vote If the quorum is lost during a meeting, the IRB cannot take votes until the quorum is restore An odd number or positions on the membership roster maximizes the number of IRB members for a given quorum requirement. Alternate members are included in the quorum vote only if they are replacing a regular member at the meeting. Initial applications, modifications, or scheduled continuing review applications may be approved or disapproved by a majority vote of the voting members present. Attendance of all participating members is recorded in the meeting minutes.

All voting is conducted in closed session, and voting privileges shall be limited to IRB members present at the meeting. Proxy votes are not accepted. Member votes are recorded by the IRB Administrator via a show of hands, and a majority vote is required for any IRB determination. Voting results will be recorded in the minutes of the meeting including the number of members voting for, against, and abstaining. The IRB Chair votes only in the case of a tie vote of the membership present at the meeting. New members do not vote at the first meeting they attend.

An IRB member may abstain from voting on a protocol as long as she/he can provide a reasonable explanation for abstaining. This abstention, and the explanation, shall be included in the minutes of the meeting. Recusals are not counted in the votes but are documented and are not counted toward the quorum.

Appeal of IRB decisions

Principal Investigators may appeal an IRB decision. by writing a letter to the IRB requesting reconsideration.

An appeal of a disapproved research project must be reviewed at a full board meeting. If an investigator wishes to appeal any other decision issued in conjunction with the review of a study, the investigator may contact the IRB for a full and considered discussion of the concern.

Concerns will be addressed by the IRB Chair in consultation with the IRB Administrator and a designated IRB member.

In the case of a decision by the IRB to disapprove, suspend, or terminate a project, the decision may not be reversed by the IO or any other officer or agency of the institution.

The IRB retains the final authority for approval of proposed research with human subjects.

IRB RECORDS REQUIREMENTS

IRB membership roster showing qualification

The ORSIRB holds an FWA, therefore, notification of IRB membership must be submitted to OHRP. The IRB Chair and Administrator will review the membership roster at least annually to ensure representation is consistent with the expertise required to adequately review the research protocols routinely submitted. Revisions to the membership roster must be registered with OHRP using their online registration procedures. Revisions must also be updated in the EMS. The membership roster will be made available in the event of an audit.

Written procedure and guidelines

Written procedures are required by federal regulation and are critical for maintaining consistency in handling protocols. These written procedures shall be revisited annually by the IRB Chair and Administrator and revised as necessary. The IRB will receive notification of the revisions. These written procedures will be made available in the event of an audit.

Minutes of meeting

The IRB Administrator records the minutes of each convened meeting of the IRB. Minutes will be posted electronically for review as soon as possible following each meeting. Minutes are reviewed by the Board at the next full board meeting. Any corrections, modifications, or additions to the minutes will be reported in the next set of meeting minutes. Minutes shall be taken in sufficient detail to show the following:

- attendance, including members (and any guests) present, as well as late arrivals or early departures by members
- actions taken by the IRB and deliberations, which are recorded without attribution
- the vote on these actions, including the number of members voting for, against, and abstaining (also recorded without attribution)
- the basis for requiring changes in or disapproving research
- the basis for requiring an approval period shorter than one year
- a written summary of the discussion of controverted issues and their resolution
- reports of unanticipated problems and adverse effect

RECORDS RETENTION

Federal Law mandates that all records related to human subjects research (HSR) be retained for a minimum of three years after study completion (defined as when data analysis is finished, not when subject participation stops). However, since 2002, DOE has had a moratorium on destroying epidemiological records for 75 years after study completion. DOE General Counsel has determined that this moratorium extends to human subjects records created and retained by researchers, but not the records retained by IRBs.

IRB Records

All official IRB records are stored indefinitely. Records before 2007 for closed studies are stored in Room 103 in Building MC-210. Inactive or closed studies as of November 11, 2014, are stored on a common drive at \\orau.net\shares\HEE\IRB_General\ORSIRB\IRBNet to IRB7 Transition\Documents. As of November 12, 2014, all active studies are in the EMS.

The IRB Administrator assigns each protocol a unique, chronological number that indicates the fiscal year and order it was received. Official IRB records for each protocol include the following:

- all documentation reviewed by the IRB,
- all correspondence related to the protocol,
- copies of press releases or media coverage of the protocol,
- notes from protocol review sessions,
- approved consent forms,
- all other documents specifically approved by the IRB relating to the protocol, (any subject recruitment material),
- progress reports submitted by the PI,
- reports of injuries to subjects,
- statements of significant new findings provided to subjects, and
- records of continuing review activities.

PI Records

The PI must retain all research-related records, including original, signed consent forms that originate with the PI or the research team for a minimum of three years after completion of the study. After three years, these records may be archived, but may not be destroyed until 75 years after completion of the study. The PI is responsible for his or her clear understanding of the retention requirements.

All documents, electronic files, videotapes, images, et, that contain the subject's personal identifiers must be kept in locked storage or access-controlled databases, with access restricted to the PI and members of the research team. All PI records must be accessible for inspection and copying by the IRB or authorized representatives of DOE or DHHS at reasonable times and in a reasonable manner. Access restrictions must continue in force until the records are destroyed. A final report may be added to the study package in the EMS if available

REFERENCES

Regulatory

10 CFR 745, Protection of Human Subjects. ["Common Rule," DOE]

21 CFR 50, Protection of Human Subjects. [Informed Consent, FDA]

21 CFR 56, Institutional Review Boards. [FDA]

21 CFR 812, Investigational Device Exemptions. [FDA]

45 CFR 46, Protection of Human Subjects, Subparts B, C, and D. [additional protection for vulnerable subjects, HHS]

DOE O 443.1B, Protection of Human Subjects.

DOE O 4300.2C, Strategic Partnership Projects (SPP)

REVISION RECORD

Issue	Page(s)	Authorized by	Changes

Acronyms

CDOEIRB-Central Department of Energy (DOE) Institutional Review Board (IRB)

CITI-Collaborative Institutional Training Initiative

CFR-Code of Federal Regulations

DHHS-U.S. Department of Health and Human Services

DOE-Department of Energy

FDA-Food and Drug Administration

FWA-Federalwide Assurance

HSP-Human Subjects Program

HSS-DOE Office of Health, Safety and Security

IAA-IRB Authorization agreements

IDE-Investigational Device Exemption

IN-DOE Office of Intelligence and Counterintelligence

IND-Investigational New Drug

IO-Institutional Official

IRB-Institutional Review Board

NNSA National Nuclear Security Administration

OHRP-HHS Office for Human Research Protections

PHI-Protected Health Information

SOP-Central DOE Institutional Review Board (CDOEIRB) Standard Operating Procedure

Definitions

Adverse event - An undesirable effect, whether expected or unexpected, that results from or is indirectly related to the entire research process (e.g., mishaps, mistakes, incorrect dosage administered, reconsideration of human subject involvement). All adverse events must be reported to the ORSIRB even if there is no obvious causal relationship between the protocol procedures and the event.

Code of Federal Regulations (CFR) - Published in the Federal Register, a publication of the Federal government that codifies the general and permanent rules for executive departments and agencies. There are 50 titles that represent broad areas subject to Federal regulation. The CFR is updated once each calendar year and is issued on a quarterly basis.

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 – For purposes of this document, "DOE" refers to the Human Subjects Research (HSP) Program Manager in the Office of Science, Washington, DC, and implies by reference the HSP Program Manager at NNSA.

DOE Human Subjects Research Database - A compilation of summary information on non-classified, non-exempt DOE research, which is available on the DOE HSRD website and updated annually.

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.

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.

Federalwide Assurance (FWA) - A written commitment from an institution to the Office for Human Research Protections (OHRP) that ensures institutional compliance with all pertinent federal regulations for the protection of human research subjects. Every institution engaged in human subjects research supported or conducted by the Department of Health and Human Services (DHHS) must obtain an FWA.

Human subject - A living individual about whom a researcher conducting research obtains:

- Data through intervention or interaction with the individual, or
- Identifiable private information or materials.

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.

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

Informed consent - The knowing consent of the human research subject, or the subject's legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or any other form of constraint or coercion.

Institutional Official – The member of Executive management who is authorized to act for the institution and assumes, the obligations in the institution's assurance to Health and Human Services' Office for Human Research Protections OHRP.

Institutional Review Board (IRB) – The generic term used in all regulations for the local body that reviews and approves human subject research.

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

Minimal risk – A risk is considered minimal if 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.

Minor – Anyone who has not yet reached the age of consent as defined by state law. This currently ranges from 14 to 18 in the US, and as low as age 12 in other countries.

Non-affiliated member – A member whose only affiliation with the institutions is serving on the Board.

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

Non-scientist – A member whose primary interest is in non-scientific areas.

Principal Investigator (PI) - The scientist or other individual designated by ORAU who is responsible for the scientific or technical direction 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 reasonable 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 researcher or associated with the information) in order for obtaining the information to constitute research involving human subjects.

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.

Principal Investigator (PI) – The researcher who was designated by his or her site senior management who is responsible for the overall direction 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.

Protected Health Information (PHI) –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.

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

Protocol review package – The minimal information required by the ORSIRB of the PI in order to conduct a review of proposed research.

Quorum – A simple majority of Board members, including at least one nonscientific member.

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.

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.
Researcher – The PI or any member of the research team involved in a study involving human subjects.
Serious Adverse Event – 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.
Unanticipated Adverse Event – 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

- 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 ORSIRB-approved research protocol, any applicable investigator brochure, and the current ORSIRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- 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 – In general, to be categorized 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 ORSIRB-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)
- Likely to place subjects or others at greater risk of harm (including physical, psychological,
- Economic, or social harm) than was previously known or recognized.

Appendix A (to be added)

Appendix B

Procedure to Determine Review Frequency

If, during the initial review of a research protocol, the ORSIRB determines that a study involves only minimal risk*, then annual review is usually sufficient. However, if the study involves **more than minimal risk**, or other factors (see Step 3 below), the following procedure is invoked.

Step	Action
1.	ORSIRB determines aspects of potential risks: • nature (physical, psychological, social, economic) • severity (moderate, high, severe) • probability (low, moderate, high) • duration (temporary, permanent)
2.	ORSIRB determines whether the following are factors in the study: • health and vulnerability of subjects involved • previously reported adverse events in similar studies • researcher and research team experience with the proposed work • PI history (causes for concern on previous research)
3.	ORSIRB assigns a review frequency that is appropriate to the risk. For example, if a study involves no more than minimal risk, but the PI has had trouble managing past studies, requiring a progress report or continuing review at 6 months may be appropriate. For another PI conducting the same study it may not be warranted. The reason for this determination is documented in the ORSIRB project file and the PI is notified of the frequency.

*The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

As an alternative (or in addition) to increased review frequency, the ORSIRB may elect to implement the following measures:

- Have an ORSIRB member monitor the consent process.
- Have an ORSIRB member or third-party observe research activities.
- Implement stronger controls to protect privacy and confidentiality.
- Interview subjects after participation.

Appendix C

Criteria for Determining Additional Monitoring

If a proposed study involves any of the following…:

A. Unusual levels or types of risk to subjects or inclusion of subjects from a vulnerable population

B. A PI or other member of the research team who previously failed to comply with the requirements of federal regulations or determinations of the ORSIRB

C. A concern about possible material changes occurring without ORSIRB approval based on information provided in continuing review or from other sources

…then the ORSIRB must seek additional monitoring (beyond reports from the PI) to verify that the approved protocol is being followed and that no material changes have occurred since the previous ORSIRB review.

The type and frequency of monitoring is determined by the following:

If research involves…	Then have an ORSIRB member or third party monitor…
Criteria A	• PI research records quarterly or semiannually
Criteria B	• research activities quarterly • consent process quarterly • PI records monthly
Criteria C	• PI records immediately • research activities immediately
More than one criteria	• PI records immediately, then monthly • research activities immediately, then quarterly

Appendix D

Reporting Table

Research Involving Human Subjects

This table summarizes what must be reported during the course of any human subject research conducted by, for, or at Sandia National Laboratories. For details on reporting responsibilities and report content, contact the ORSIRB Administrator at ORSIRB@orau.org.

"Immediate" and 24-hour reporting must be done via phone or in person, and followed up with a written description via e-mail within a reasonable time. All other reporting must be done in writing.

Who	Reports What	To Whom	When
PI	Any ***adverse event***[1]	ORSIRB	within 5 work days
	Any ***serious adverse event***[2]	ORSIRB, sponsor	immediately
	Any ***unanticipated problem***[3]	ORSIRB	within 24 hrs
	Loss or potential compromise of PII	ORSIRB, sponsor	immediately
	Deviation from approved protocol[4]	ORSIRB	within 24 hrs
	Failure to comply with requirements[4]	ORSIRB	
	Proposed change in approved protocol, including change of PI[5]	ORSIRB	before change occurs – change must be approved by ORSIRB
	Progress and status on active protocols[6]	ORSIRB	annually, unless otherwise directed by the ORSIRB
ORSIRB	All serious adverse events[7]	ORAU, DOE, sponsor	within 24 hrs
		OHRP	within 1 week
	All unanticipated problems[8]	ORAU, DOE	within 48 hours
		OHRP, sponsor	within 30 days of receiving PI report
	All ***serious*** or continuing ***non-***	ORAU, DOE,	within 24 hrs

Who	Reports What	To Whom	When
	compliances[9]	ORAU, sponsor	
	All suspensions or terminations of ORSIRB approval of research[10]	PI, ORAU, DOE, OHRP	within 24 hrs
	Loss or potential compromise of PII	ORAU, DOE	immediately
	Any new proposal that includes:[11] • an institution without an IRB • a foreign country • a potential for significant controversy • HTM • vulnerable populations *or* • classified or sensitive information	DOE	before ORSIRB approval
	Changes in ORSIRB membership[12]	OHRP	as they occur
	Complaints about research[13]	ORAU, DOE	within 5 work days
	Summary of approved research[14]	DOE	annually

DOE – Human Subject Protection Program Office (SC-72) and local DOE Office (SSO) as needed

ORSIRB – Human Studies Board Administrator ORSIRB@orau.org

HTM – Human Terrain Mapping

OHRP –Office for Human Research Protections in the Department of Health and Human Services

ORAU – ORAU Institutional Official

PI – Principal Investigator

PII – Personally Identifiable Information

Definitions

Adverse event – Any undesirable incident, experience, or outcome associated with a subject's participation in the research, whether or not considered related to the research.

Serious adverse event – An adverse event that meets **any** of the following criteria

- results in death
- is life-threatening
- results in subject hospitalization
- results in persistent or significant disability/incapacity or other harm
- results in congenital anomaly/birth defect, or
- requires medical or surgical intervention to prevent one of the above outcomes

Noncompliance – Any failure to comply with applicable requirements (federal law, DOE directive, or ORSIRB policy/procedure) to protect human subjects.

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 14 DOE O 443.1B 3-17-2011 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.).

Serious noncompliance – A noncompliance is deemed serious if it affects the health, safety or well being of subjects, or if it constitutes a deviation from the ORSIRB-approved protocol.

Continuing noncompliance – A noncompliance becomes continuing if it is repeated or additional noncompliance is associated with the same PI or organization.

Unanticipated problem -- Any incident, experience, or outcome associated with the subject's participation in the research that meets **all** of the following criteria:

- is unexpected given the research procedures and the subject population being studied
- is possibly related** to participation in the research
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

**there is a reasonable possibility this may have been caused by the research procedures

Examples

Unanticipated Problem

A PI conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the PI's car on the way home from work. This constitutes an unanticipated problem and must be reported because the incident was (a) unexpected (the PI did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of harm from the breach in confidentiality of the study data than was previously known or recognized.

Adverse Event that is Not Unanticipated

A PI is conducting a psychology study to evaluate the factors that affect reaction times in response to auditory stimuli. To perform the reaction time measurements, subjects are placed in a small, windowless, soundproof booth and asked to wear headphones. The ORSIRB-approved protocol and informed consent document describe claustrophobic reactions as one of the risks of the research. The 20th subject enrolled experiences significant claustrophobia, resulting in the subject withdrawing from the research. This is not an unanticipated problem because the potential for claustrophobic reactions – in terms of nature, severity, and frequency – was expected and documented. This is reportable to the ORSIRB, but not to DOE or OHRP.

Source of requirements identified in table

[1, 2, 3] 10 CFR 745.103(b)5, DOE 443.1B
[4] 10 CFR 745.103(b)5
[5] 10 CFR 745.103(b)4, DOE 443.1B
[6] DOE 443.1B
[7] 10 CFR 745.103(b)5, DOE 443.1B
[8] 10 CFR 745.103(b)4 and 5
[9] 10 CFR 745.103(b)5
[10] 10 CFR 745.103(b)4 and 5
[11] DOE 443.1B
[12] 10 CFR 745.103(b)3
[13] DOE 443.1B
[14] DOE 443.1B
PII - DOE 443.1B, DOE O 206.1, DOE M 471.3-1, DOE M 205.1-8

Notes

- This table does not include FDA requirements.
- Some reporting requirements vary with the funding source.
- These definitions and time frames are a compilation from several sources, including the OHRP Guidance issued 1/15/07.
- Terms like “promptly” and “immediately” are a little vague, but still connote a limited time span. The intent seems to be to allow a bit of wiggle room for both PIs and IRBs while still conveying a sense of urgency.

For additional information, see OHRP Guidance on reviewing and reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events.