Central Beryllium Institutional Review Board
Standard Operating Procedures

7/08

- Administrator Records

Chapter 10 REFERENCES

Chapter 11 DEFINITIONS

CHAPTER 1: PURPOSE, BACKGROUND, AND SCOPE

Purpose

The purpose of this manual is to document the operating procedures of the Department of Energy Central Beryllium Institutional Review Board (CBeIRB), hereinafter referred to as the CBeIRB, or the Board. The function of the CBeIRB is to assure that the risks to human participants involved in Beryllium (Be)-related studies sponsored or funded by Department of Energy (DOE) facilities are minimized and reasonable in relation to the anticipated benefit, and to protect the rights and welfare of study participants in accordance with applicable federal regulations, state laws, DOE directives, existing ethical principles and professional practice standards, and institutional policies.

Background

The CBeIRB was established in 2001 and is funded by the DOE Office of Science (SC), and the Office of Health, Safety and Security (HSS); see DOE-Wide Central IRB to Review Beryllium Research. The CBeIRB serves as DOE's IRB of record for purposes of satisfying the human subjects protection requirements of the DOE and US Department of Health and Human Services (DHHS) for study protocols that involve employees of DOE or its contractors and/or are explicitly funded by DOE or other agencies or institutions as Beryllium (Be) research or surveillance. The CBeIRB is specifically responsible for review and approval of Be-related human subjects research in the following areas:

- Be-related research involving human subjects (and beryllium) that is funded by the Department of Energy regardless of the source of the human subjects or the affiliation of the researchers.

- Be-related research carried out by DOE or DOE contractor employees that involves beryllium and human subjects regardless of funding source or source of subjects and their status with respect to Be exposure or disease.

- Be-related research involving current or former DOE or DOE contractor employees regardless of the source of the funding if the subject pool is specifically defined as DOE or DOE contractor employees or former employees.

- The beryllium screening component of the Former Worker Medical Screening Program, and any site or off-site research activities related to beryllium exposure, medical testing, or pathogenesis of chronic beryllium disease.

Specifically excluded from this policy are activities related to DOE site-specific medical surveillance of its current workers under the DOE Chronic Beryllium Disease Prevention Program Final Rule, 10 CFR 850. Any Be study or activity involving human subjects not covered by 10 CFR 850 shall be referred to the CBeIRB to determine its need to be reviewed by the Board.

Within D0E, SC is responsible for making final decisions as to what constitutes DOE-related human subject research and how human research subject protection must be implemented. When

questions or uncertainties arise regarding the applicability of human subjects protection regulations to research, the final resolution is made by the DOE Human Subjects Program Manager at 301-903-7693.

History

Since the Manhattan Project era, the Department of Energy (DOE) and its predecessor agencies have had the obligation and responsibility, under the Atomic Energy Act of 1954, to protect the health of its workers. The prevalence of chronic beryllium disease (CBD), as a result of the use of beryllium (Be) in weapons production and research, has been increasing across the DOE complex. This has sparked an increased awareness of and concern about this serious occupational illness and has resulted in DOE-wide beryllium sensitivity testing of current and former workers, the publication and implementation of DOE's Chronic Beryllium Disease Prevention Program Final Rule, 10 CFR 850, and an expanded beryllium disease research program.

DOE was directed, in 1993, through Section 3162 of the National Defense Authorization Act for Fiscal Year 1993 (Public Law 102-484), to develop a program of medical evaluation to identify occupationally related health impacts in former DOE workers. DOE initiated several medical evaluation programs prior to 1993 including a beryllium medical surveillance program for former Rocky Flats and Y-12 workers and a medical surveillance program for former radiation workers at the Rocky Flats Plant. Subsequent to 1993, DOE initiated the Nationwide Former Beryllium Workers Medical Surveillance program and 15 other site-specific surveillance projects at 12 DOE sites.

Rationale for a Central Beryllium Institutional Review Board (CBeIRB)

DOE is obligated to ensure that research related to beryllium exposure, to beryllium medical testing, and to understanding the pathogenesis of berylliosis is conducted in accordance with the highest prevailing ethical standards. Adherence to this obligation is vital because of the potential impact on quality of life of the beryllium-exposed workforce, namely: employability, insurability, health status, and privacy.

Heightened sensitivity to the information given and support offered to workers before participation in beryllium research is essential to allow the worker to make informed choices about such participation. Because of the potential for significant social and economic hardship to the worker resulting from diagnosis issues or loss of confidentiality, IRB review and approval of beryllium research protocols is required before any workers can be asked to participate in the research activities.

The requirement for IRB approval poses a problem at some DOE sites that have workers exposed to beryllium but have no IRB. Even if the DOE site or DOE-funded grantee has access to an IRB, that IRB may have insufficient experience with beryllium-related research to adequately evaluate issues concerning protection of human subjects.

The purpose of the CBeIRB is to provide the DOE workforce, DOE, DOE contractors, and any organization(s) engaged in research on beryllium exposure, testing, or occupational disease funded by DOE and/or involving the DOE workforce with expertise and consistency in addressing human subjects protection issues.

Definition and Scope of the CBeIRB

The Office of Science (SC), with support from the Office of Health, Safety, and Security (HSS), consistent with responsibilities in 10 CFR 745, Protection of Human Subjects and Department of Energy DOE 443.1A, Protection of Human Subjects, supports the CBeIRB.

The CBeIRB is administered by Oak Ridge Associated Universities (ORAU) under a Federal-Wide Assurance (FWA 00005031) with the Office of Human Research Protection (OHRP) of the DHHS, consistent with responsibilities in 10 CFR 745, Protection of Human Subjects and Department of Energy Policy DOE 443.1A, Protection of Human Subjects .

Reconciling the need to conduct timely beryllium research at DOE sites with the equally compelling need for review of the beryllium research protocols by the site IRB and the CBeIRB presents unique challenges. This need for coordination is especially true when a beryllium research protocol is conducted by a grantee whose institution has its own IRB. For this reason, time requirements have been established for the review process to allow for site IRB and CBeIRB review.

CHAPTER 2: INTRODUCTION AND OVERVIEW OF IRB FUNCTIONS

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

- The Nuremberg Code
- The Declaration of Helsinki
- The Belmont Report

Basic Ethical Principles

The CBeIRB 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." These three principles are:

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.

Beneficence: requires that researchers (and their institutional organizations) create benefits for participants and society. 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.

Overview of IRB Responsibilities: Criteria for IRB Approval of Research Involving Human Subjects

Role of IRBs

All domestic and foreign institutions or sites where research involving human subjects is conducted or supported by the Department of Health and Human Services (DHHS) are required to perform this research in keeping with Federal regulations, Title 45, Part 46 of the Code of Federal Regulations, Protection of Human Subjects (45 CFR 46), or other ethical standards that provide equivalent protections, a determination made by the DHHS Office of Human Research Protections (OHRP). DHHS 45 CFR 46 requires prospective and continuing review and approval of human subjects research activities by a committee, usually called an Institutional Review Board (IRB). The primary mandate of IRBs is to protect the rights and welfare of humans who are the subjects of research. In fulfilling this mandate, the 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

IRB Review of Research Activities Involving Human Subjects

Federal regulations allow an IRB to approve research only after it has determined that all of the following requirements are satisfied:

1. Risks to subjects are minimized by using procedures that are consistent with sound research design, and that do not unnecessarily expose subjects to risk. Whenever appropriate, researchers should employ procedures that are being performed on subjects for diagnostic or treatment purposes.

2. Risks to subjects are reasonable relative to

    a. anticipated benefits, if any, to subjects, and

    b. the importance of the knowledge that may reasonably be expected to result.

3. The selection of subjects is equitable. In making this assessment the IRB must take into account the purposes of the research and the setting in which it will be conducted. The IRB must be particularly attentive to the special problems that may arise when research involves vulnerable populations, such as children, pregnant women, prisoners, mentally disabled persons, or economically or educationally disadvantaged persons. If any of the subjects is likely to be susceptible to undue influence or coercion, the IRB may require additional safeguards in the study to protect such subjects.

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 45 CFR 46.116) and that they are understandable to a lay person.

5. The research plan makes adequate provisions for ensuring the safety of subjects.

6. There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

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

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

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?
7. Subject privacy & confidentiality are maximized.	(a) Will personally-identifiable research data be protected to the extent possible from access or use? (b) Are any special privacy & confidentiality issues properly addressed, e.g., use of genetic information?
Additional considerations	
1. Ionizing radiation.	If ionizing radiation is used in this protocol is it medically indicated or for research use only?
2. Collaborative research.	Is this domestic/international collaborative research? If so, are FWAs or other assurances required for the sites involved? Is there a CRADA?
3. FDA-regulated research	Is an IND or IDE involved in this protocol?

Risk/Benefit Assessment

Risk

Regulatory definition of minimal risk: Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(h)(i)).

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

Benefit

Definition: A research benefit is considered to be 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 to be a benefit, but rather compensation for research-related inconveniences.

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

CHAPTER 3: AUTHORITIES AND RESPONSIBILITIES

ORAU

ORAU has established and shall operate and maintain the CBeIRB for DOE/SC and HSS in accordance with 45 CFR 46 DHHS Protection of Human Subjects and 10 CFR 745 DOE Protection of Human Subjects. ORAU will provide meeting and records keeping space for the Board, and sufficient staff and technical resources to support the Board in carrying out its duties and meeting. ORAU will maintain a current Federal Wide Assurance (FWA) with DHHS.

Institutional Official (IO)

The President, ORAU, is the Institutional Official responsible for the continuation of the FWA under which the CBeIRB operates. The Institutional Official provides written appointment letters designating the Institutional Representative, the Chair, and the individual Board members (see below). The President of ORAU has the responsibility to provide the support and resources necessary to ensure the effective operation of the CBeIRB, as well as overseeing the overall quality and efficiency of the Board's performance.

Designated Institutional Representative (DIR)

The Institutional Official may appoint an individual to serve as the Designated Institutional Representative (DIR) to the Board with responsibility to the President for liaison between the CBeIRB and ORAU. The person who serves as the DIR must be provided with written authorization by the President of ORAU to assume these responsibilities. The DIR serves as a non-voting participant at CBeIRB meetings. The DIR reviews policy and assures the ORAU President that policy contains appropriate guidance for ORAU oversight and compliance responsibilities.

CBeIRB Administrator

The CBeIRB Administrator is responsible for managing the day-to-day activities of the CBeIRB and is the primary point of contact and liaison between the CBeIRB and ORAU. The Administrator's responsibilities include:

- Acts as point of contact and subject matter expert concerning the CBeIRB for DOE, other federal agencies, and the Be research community.
- Manages the administrative and record-keeping requirements of the CBeIRB.

- Ensures that CBeIRB activities are documented, and minutes of meetings are generated and maintained.
- Facilitates education in compliance with federal agency and institutional requirements.
- Schedules and coordinates initial and continuing reviews.
- Reviews all submitted materials for completeness and makes recommendations for level of review required; distributes materials to Board members.
- Informs PIs of review outcomes.
- Schedules meetings of the full Board and others as needed.
- 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 CBeIRB Secretary of Record responsible for recording the minutes of meetings, preparing the official meeting record, and maintaining CBeIRB records and files.

CBeIRB Chair

The Chairperson (Chair) is responsible to provide professional leadership and for ensuring that the Board carries out its responsibilities. Some Chair responsibilities include:

- Determines the type of review required (Full Board, Expedited, Exempt).
- Conducts expedited reviews or appoints voting member(s) of the Board to expedited review subcommittees.
- Performs Chair functions at all meetings.
- Determines final disposition of all protocols reviewed by the Board.
- Mentors all new and established Board members.
- Collaborates with PIs and / or Chairs or members of other IRBs as necessary.
- Does not vote except in the case of a tie in the membership vote.

CBeIRB Members

Members of the CBeIRB are expected to:

- Complete initial required training following appointment.
- Complete refresher training as required.
- Attend scheduled meetings.
- Review all materials distributed by the Administrator prior to scheduled meetings.
- Participate as primary or secondary reviewers or expedited reviewers when asked to do so by the Chair, Vice Chair, or Administrator.
- Perform other IRB-related activities when requested by the Chair, Vice Chair, or Administrator.

Principal Investigators

Principal Investigators (PI) on projects subject to review and approval by the CBeIRB have primary responsibility for protecting the rights and welfare of human research subjects and for complying with all applicable provisions of federal law, any special requirements of the DOE, and any requirements set by the Board. Each PI must be familiar with the ethical principles of human subjects research and the requirements of federal regulations, DOE directives, and applicable state laws. The PI also has the following responsibilities:

- Justifies the need to involve human subjects in Be-related research.
- Assures that all risks to such subjects associated with the protocol are understood and clearly communicated.
- Secures authorized institutional official approval of Be proposals involving Be research prior to CBeIRB review.
- Ensures that each potential subject understands the nature of the research.
- Provides a copy of the CBeIRB-approved informed consent document to each participant at the time of consent unless the CBeIRB has specifically waived this requirement.
- Assures that all signed consent documents are retained in accordance with the terms of DOE's contract or grant or DOE's applicable records retention schedules if DOE is not the funding source.
- Assures that subject privacy and data confidentiality are protected in so far as allowed by law.
- Promptly reports any proposed changes in previously approved research to the institutional IRB, the local site IRB (if applicable), the CBeIRB, and does not initiate changes without approval by all engaged IRBs.
- Reports progress of approved research to the CBeIRB as often as, and in the manner prescribed by, the CBeIRB, but not less than once a year.
- Promptly reports to the local site IRB (and institutional IRB if applicable) any unanticipated injuries or problems involving risks (adverse events) to subjects or others and immediately forwards a copy of the report to the CBeIRB.
- Notifies the CBeIRB when the project is complete or needs to be inactivated.
- Notifies the Food and Drug Administration (FDA) and the Board whenever it is anticipated that a Be-related investigational new drug (IND) or device exemption will be required.
- Submits required materials to CBeIRB for review and approval.
- Assures that research is conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA) requirements when appropriate.
- Provides evidence of professional credentials (CV or resume) and required training in Human Subjects Protection for self and key members of the research team prior to commencement of research activities.

CHAPTER 4 CBeIRB STRUCTURE

Membership

An IRB must have at least five members with varying backgrounds to promote complete and adequate review of human research activities commonly conducted by institutions (10 CFR 46). The CBeIRB members must be sufficiently qualified in expertise, experience, and diversity of background. This should include attributes such as racial and cultural heritage, sensitivity to community attitudes to adequately promote respect for its advice and counseling in safeguarding the rights and welfare of human subjects involved in Be-related research. CBeIRB members must assess the acceptability of proposed Be-related research in terms of institutional regulations, applicable law, and standards of professional conduct.

The CBeIRB must include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are nonscientific. The CBeIRB must also include at least one member who is not affiliated with the institutions and who is not an immediate family member of a person affiliated with the institutions that currently are conducting or propose to conduct Be-related research.

The Board must have both male and female members.

The Board must have at least one member who represents the interests of the community at large.

Membership of the CBeIRB is broadly based and include representatives from all stakeholders in the beryllium research community. To capitalize on the experience of IRBs located at DOE sites (site IRBs) with a history of beryllium research, one member from each of three site IRBs serves a 3-year renewable term on the CBeIRB.

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

Voting members shall be appointed to serve renewable 3 year terms. Term renewal is at the discretion of the full Board Board members and all non-voting representatives to the Board may nominate persons for membership to the Board. All members of the Board will be polled to vote on potential new members; the approval of a simple majority is required. Formal appointment (in writing) to the Board shall be made by the IO. .

The Board shall nominate an active or former member to serve as its Chair for a 3-year term; additional terms may be served at the discretion of the Board membership. All voting members of the Board will be polled to vote on the nomination for Chair; the approval of a simple majority of all the voting members is required. The IO shall make formal appointment of the Chair in writing following the outcome of the Board members' vote.

The Board shall nominate an active or former member to serve as the Vice-Chair for a 3-year term; additional terms may be served at the discretion of the Board membership. All members of the Board will be polled to vote on the nomination for Vice- Chair; the approval of a simple majority of all the voting members is required. The IO shall make formal appointment in writing following the outcome of the vote. The Vice-Chair has the authority to act for the Chair in his/her absence.

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.

Resignation/Termination of Members

Members may resign from the CBeIRB at any time, but fulfilling existing terms is encouraged.

Termination by the Institutional Official of a member from the CBeIRB prior to expiration of his or her term requires documented "just cause" to show that continuation or renewal of a member's term would be detrimental to the Board. Just cause for removal may include, but is not limited to, lack of attendance, misconduct, unresolved conflict of interest, failure to complete required training (see below) or failure to complete work as assigned or requested by the Chair, Vice-Chair, or Administrator.

Member Training

Members are required to successfully complete Human Subjects' training following appointment to the Board. The records of this required training will be maintained for individual members by the CBeIRB Administrator. Maintenance of other relevant training records is the responsibility of individual members. Refresher training is required at least every three years.

Time is allocated on the agenda during each meeting to educate members and to address current issues and pending changes in regulations. The CBeIRB Administrator, Chair, or members also may use this time to disseminate information obtained from national meetings and conferences attended during the year.

CHAPTER 5: REVIEW AND APPROVAL

It is DOE policy that all Be-related research involving human subjects conducted by employees of DOE or its contractors and/or are explicitly funded by DOE or involves present or former DOE workers or contractor employees or employees of certain DOE vendors be reviewed and approved by the CBeIRB prior to the commencement of research activities. Within the Department, the Office of Science (SC) is responsible for making final decisions as to what constitutes DOE-related human subject research and how human research subject protection must be implemented. When questions or uncertainties arise regarding the applicability of human subject's protection regulations to research, the final resolution will be made by the DOE Human Subjects Protection Program Manager.

The CBeIRB serves as the IRB of record for purposes of satisfying the requirements of DOE and DHHS for review of Be study protocols in which current DOE workers, DOE-contractor workers, employees of current or former DOE vendors, or former workers are included in the study population when the protocol includes Be components or is explicitly funded as Be research. When the protocol is primarily a non-beryllium effort, the CBeIRB will focus its effort on review only of the beryllium components. Examples include Former Beryllium Workers Medical Surveillance Programs, the beryllium screening component of the Former Workers Medical Screening Programs, and

any site or off-site research activities related to beryllium exposure, medical testing, diagnosis, or pathogenesis of chronic beryllium disease not covered by 10 CFR 850.

Initial Review of New Studies by CBeIRB

The DOE Office of Science (SC) and the CBeIRB shall be notified by the PIs' institutions of all new proposals to conduct Be-related research studies or projects that involve DOE workers as subjects or participants or other persons that are sponsored at DOE sites by DOE or other federal agencies. Awareness of this responsibility is developed through specified job duties and mandatory training in human subjects protection within the PI's institution and outreach and educational programs provided by DOE/SC and the CBeIRB.

Only the CBeIRB Chair (or in the event of a dispute, DOE/SC) will determine whether or not the proposed Be activity requires review and approval by the CBeIRB, as well as the level of review required, or whether to exempt a protocol from CBeIRB approval. These determinations will be communicated to the PI by the CBeIRB Administrator.

When the CBeIRB's approval of a protocol is final, the PI will provide a copy with "tracked changes" and clean / final copy of all revised documents as approved, to the CBeIRB Administrator. The date and duration of CBeIRB approval must be noted on all consent forms and any other documentation provided to participants.

Continuation Review

Federal regulation 45 CFR 46.109 (e) requires that approved protocols be periodically reviewed to ensure the continuing protection of human subjects over the course of the research. The scheduling of these reviews should be appropriate to the level of risk involved in the study but must be no less than every 12 months. The CBeIRB administrator will notify the PI sixty (60) days in advance of the scheduled date of continuation review of each protocol. As with the initial review of new protocols, the continuation review may be conducted either by the full Board or by an expedited mechanism, depending on the level of risk involved in the research and as outlined in 45 CFR 46. The PI will be notified of the level of review required. Materials to be supplied by the PI to the Administrator of the CBeIRB for continuation review are listed in Continuing Review - Application to Involve Human Subjects in Research .

Protocols Requiring Initial or Continuing Reviews by Multiple IRBs

DOE-related beryllium research may be subject to review by both the local (site or institutional) IRB of the principal investigator before submission to the CBeIRB. Arrangements will be made on a case-by-case basis to maximize the efficiency of initial and continuing reviews of individual Be-related research studies/projects by multiple IRBs through discussions between the CBeIRB and the other IRBs involved.

For new proposals these discussions will be initiated by the CBeIRB Administrator when notice of the proposed Be-related study/project is received from the PI or from DOE. The objective of the discussions will be to establish the process and timetables for the initial and continuing reviews of the protocol and to define the other responsibilities of the various IRBs.

For continuation reviews, the responsibility for continuation approval will rest with the DOE site IRB and the PI's Institutional IRB. The CBeIRB will only review protocols for continuation if there has been a change to a beryllium component or if there has been an adverse event related to a beryllium component.

Levels of Review

The length of time required for review of an application is necessarily dependent on the review category into which a given application falls. In general, based on an assessment of the risks and benefits, complexity of the protocol, and quality and completeness of the information provided, IRB review may be accomplished in as little as a day for exempt protocols or from 4-8 weeks for expedited or full Board review.

Federal regulation 45 CFR 46 allows for three levels of review: (1) exempt, (2) expedited, and (3) full Board. The level of potential risk to the subjects determines the level of review required. The higher the risk, the greater the rigor of review. The Chair, Vice Chair, or Administrator of the CBeIRB reviews all protocols submitted for review to determine the appropriate level of review required considering any recommendations made by the PI, DOE site, or other institutional IRBs. The Chair, CBeIRB will make the final determination regarding the level of review the protocol requires.

Exempt Review

Certain low-risk research activities are exempt from rigorous IRB review; however, the CBeIRB Chair or Vice-Chair must conduct a preliminary review to determine whether the research meets the criteria for exemption. Regardless of the determination of the DOE site IRB and the institutional IRBs, the final determination shall be made by the CBeIRB. Exempted proposals are included on the agenda of the next full Board meeting for concurrence and to ensure they are noted in the minutes of that meeting. In the absence of concurrence by all voting members of the Board, the protocol will be reviewed by the full Board at that meeting or designated for expedited review.

Expedited Review

An expedited review, rather than requiring the consideration of the full CBeIRB at a convened meeting, may be conducted by the CBeIRB Chair, Vice Chair, or a designated voting member, or a group of voting members designated by the Chair. Following an expedited review, the CBeIRB Chair may approve a proposal, ask for modifications, or refer it to the full Board.

To be considered for expedited review, proposed research must meet two conditions:

(1) It must present no more than *minimal risk* to subjects, and
(2) It must fit into one of the identified research categories.

Expedited review may also be used for minor changes to approved research and for continuation reviews of previously approved protocols. The requirements for approval of a protocol under the expedited review mechanism are the same as those which apply to a full Board review (e.g. sound scientific protocol, proper informed consent procedures, minimization of research risks, etc.). The

only difference is that an expedited review may be performed by the Chair, an assigned Board member, or group of Board members, whereas higher risk studies require deliberation by the full Board.

When the expedited review procedure is used, Board members are informed by including those projects on the agenda for discussion at the Board's next meeting. At a convened meeting, any member may request that an activity that has been approved under the expedited process be reviewed by the full Board in accordance with non-expedited procedures

Proposed research cannot be disapproved under expedited review procedures.

Full Board Review

All other human subject research subject to CBeIRB review requires review at a convened meeting by a valid quorum of CBeIRB members. This is the highest level of review and to be approved, proposed research must receive the approval of a majority of those voting members present (a valid quorum must exist at the time the vote is taken). All initial, continuation reviews, and protocol amendments requiring full Board review shall be conducted at convened meetings. Research protocols scheduled for full Board review shall be distributed to all members of the Board at least 10 working days prior to the meeting.

Conflict of interest note: No CBeIRB member may participate in the review of any project in which he or she has a conflicting interest, except to provide information requested by the IRB. Board members who have active affiliations with the participating institutions shall not be eligible to vote on protocols/consent forms submitted by investigators (PIs or Co-PIs) at the institutions with which the members are affiliated, nor to serve as Primary or Secondary reviewers of such protocols.

If the Board Chair determines that expert consultants are required to advise the Board in its review of a protocol, the protocol in question shall also be distributed to the appropriate consultants or experts for review prior to the meeting. Their presence at the meeting as non-voting attendees or their written comments regarding the protocol will be invited, whichever is more appropriate; the consultant's opinions will be considered by the Board in reaching it disposition on the protocol.

If warranted, CBeIRB meetings may be convened and conducted via electronic (virtual) conferencing methods. Such events will be recognized as a "convened" meeting provided that each participating CBeIRB member has received all pertinent material prior to the meeting, and can actively and equally participate in the discussion of all protocols. Minutes of such meetings must clearly document that these two conditions have been satisfied in addition to the usual regulatory requirements (e.g., attendance, initial and continued presence of a majority of voting members, including at least one nonscientist member; actions taken by the IRB; the vote on such actions; discussion and resolution of controversial issues).

The presence of a simple majority of the voting membership of the Board constitutes a quorum and is required in order to convene a meeting for the review of research protocols. The quorum must be maintained during the voting process in order to record a valid voting determination. For a research protocol to be approved it must receive the approval of the majority of the established quorum of voting members present at the convened meeting.

Primary/Secondary Reviewers

The CBeIRB may use the primary / secondary reviewer system for all protocols requiring full Board review; primary and secondary reviewers will be selected on an as needed basis by the Chair or the Administrator. Both reviewers shall perform an in-depth review of all pertinent documentation and submit review comments in writing for distribution to members at the meeting. All other CBeIRB members should receive and review the protocol documents (in sufficient detail to make the determinations required under DHHS regulation 45 CFR 46.111), the proposed informed consent document, and any advertising/promotional material(s). Primary and secondary reviews should point out and discuss all relevant issues, they should make a written recommendation to the Board, based on their review.

Materials to be Submitted to the CBeIRB for New Protocol Review

Principal Investigators shall prepare protocols giving a complete description of the scientific and ethical aspects of proposed research, including provisions for the adequate protection of the rights and welfare of prospective research subjects and ensuring compliance with applicable laws and regulations. This is required even in situations in which the research is exempt under 45 CFR 46.101. The proposal review package must include the following elements for the initial review (continuing review requirements are addressed elsewhere).

- Project protocol (including background and rationale for the study, details of the scientific design and methodologies, human subject's protection methodologies, sampling plan/statistical design, data management, data security/confidentiality, dissemination and notification plan, recruiting materials). Note: these items are included in the Application for Review .
- Any copies of supporting technical/peer reviews, internal or external, of the protocol.
- Current protocol or project handbook (to include all current local site and CBeIRB-approved consent forms, fact sheets, data collection instruments).
- Documentation of compliance with HIPAA provisions for research, when required (copies of local / site IRB-approved authorizations from participating covered entities).
- Informed Consent document and procedure.
- Standardized information sheets or proposed alternative information sheets.
- Documentation of DOE-required special conditions.

Informed Consent

Investigators shall include with the protocol all applicable informed consent documents that address all the elements of informed consent as prescribed in 45 CFR 46, section 116, and other elements required by the DOE/SC or CBeIRB to be included in a consent form. Principal Investigators are responsible for ensuring that legally effective informed consent documents shall:

- Be obtained using a consent form that has been reviewed and approved by the DOE site IRB, the Institutional IRB, and CBeIRB within the previous 12 months or less.
- Be obtained from the subject or the subject's legally authorized representative.
- Be in non-technical language 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.
- Be obtained under circumstances that offer the subject or the representative sufficient opportunity to consider whether the subject should or should not participate.
- 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 releases or appears to release the Principal Investigator, the sponsor, the institution or its agents from liability for negligence.

When the documentation requirement is waived, the Board may require the PI to provide subjects with a written statement regarding the research.

Waiver or Alteration of Informed Consent

At the request of the PI, the CBeIRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in 45 CFR 46.116 (a) and (b), or waive the requirement to obtain informed consent provided the Board finds and documents that:

- The research is to be conducted for the purpose of demonstrating or evaluating federal, state or local benefit or service programs that are not themselves research programs; or, procedures for obtaining benefits or services under these programs, or possible changes in or alternatives to these programs or procedures.
- 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 he/she wants documentation linking him/her with the research and his/her 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 the research context.
- The waiver or alteration will not adversely affect the rights and welfare of the subjects
- The research could not practicably be carried out without the waiver or alteration.
- Whenever appropriate the subjects will be provided with additional pertinent information after participation.

Disposition of a Protocol Following CBeIRB Review

When the CBeIRB reviews a proposed protocol, it has four options:

- **Approve**: Protocol is approved as submitted.
- **Conditional Approval (see below):** Protocol requires modifications or PI must furnish additional information.
- **Table:** Protocol needs major revision or rework before the CBeIRB can complete review or the Board has unresolved questions and the PI is not available to address them.
- **Disapprove:** Protocol does not meet the minimum criteria required for approval.

To approve a research study, the CBeIRB must ensure that all the following requirements have been satisfied:

- Risks to subjects are minimized and reasonable in relation to anticipated benefits.
- Selection of subjects is equitable.
- Participation is voluntary, and informed consent will be sought and appropriately documented, unless the need for obtaining or documenting informed consent has been specifically waived.
- 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.

Conditional Approval

If the CBeIRB grants conditional approval pending changes to the proposal, such changes must be completed before the CBeIRB Chair will certify final approval of the proposal. Alternatively, the CBeIRB may approve, but impose certain restrictions or conditions on the researchers or on the conduct of the research. In all conditional approval cases, the research team will be given a limited time period in which to respond to the satisfaction of the Board.

Conditional approval requires three steps:

1. CBeIRB specifies conditions (in writing to the PI). A letter is prepared by the CBeIRB administrator for the Chair's signature.
2. PI meets conditions set requested by the Board and provides documentation to the CBeIRB within a reasonable time as established by the Board.
3. CBeIRB verifies (usually by the Chair) that conditions have been achieved. If verification cannot be made, the proposal cannot be approved.

Table

When a protocol is reviewed by the full Board at a convened meeting, and Board members determine that the information provided is inadequate for Board members to make a determination, the protocol will be tabled and the PI notified that further documentation is required. The PI is also

informed that no work or recruitment of subjects may begin until adequate revisions have been received and reviewed for approval by the full Board at its next scheduled meeting.

Disapprove

If a study is disapproved, the CBeIRB Administrator notifies the PI in writing and must specify the reason(s) for the disapproval so the investigator has an opportunity to respond (in person or in writing). Investigators have the right to request the CBeIRB to reconsider research disapproved proposals, with or without modifications.

Approval Period

When the CBeIRB approves a study, it must also determine how often it needs to be re-reviewed. The maximum approval period is for 12 months and is granted to studies that are determined to be no greater than minimal risk. Studies that have potential for greater than minimal risk shall be evaluated on a case-by-case basis, and review frequency shall be determined by considering factors such as the health and vulnerability of subjects involved, previously reported adverse events, and investigator/group experience with the proposed work.

Notice of Approval

When all CBeIRB conditions for approval have been satisfied, the CBeIRB Administrator prepares an approval letter that specifies the CBeIRB approval date and the date that approval expires. This notice also includes the requirements the PI must meet while conducting the research.

Documentation

After CBeIRB approval and before beginning research, the PI must be able to show that the proposed research and consent documents have been reviewed and approved by the CBeIRB, all subjects are fully informed, and that their consent has been documented in signed consent forms (unless the informed consent requirement was specifically modified or waived by the CBeIRB

Frequency of Review

The Board shall determine, in its initial review of research protocols, the schedule for continuation review. Such a determination will be made by the Board based primarily on the nature and magnitude of the risk(s) of the research to the subjects. The minimum requirement is annual. For all approved protocols, the PI will be notified of the schedule for follow-up continuation review.

Collaborative Projects

45 CFR 46 permits cooperative research projects involving more than one institution and potentially more than one IRB. With the approval of DOE, an institution participating in a cooperative project may enter into a joint review arrangement, may rely upon the review of another institution's qualified IRB, or may make similar arrangements to avoid duplication of effort. When conducting coop-

erative research, each participating institution is responsible specifically for safeguarding the rights and welfare of the human subjects involved.

International Projects

International Projects shall be in conformance with applicable regulations (e.g., 45 CFR 46.101(h) and 10 CFR 745 §101(h)).

CHAPTER 6: POST-APPROVAL EVENTS AND ACTIONS

Amendments/Modifications to an Approved Protocol

The PI shall submit a completed Modification Form for all proposed modifications or amendments to an approved protocol shall be submitted to the CBeIRB administrator to initiate CBeIRB review and approval prior to their implementation. As with other reviews, the review of modifications to an existing protocol may be conducted by either the full Board or the expedited mechanism depending on the level of risk involved and the scope of the proposed changes. Final determination of the level of review required will be determined by the Chair, CBeIRB. Changes to an approved protocol shall not be implemented without approval from the CBeIRB.

Completion/Termination

When a study is completed or the PI wishes to terminate it, the PI must notify the CBeIRB, at which time the protocol will be placed on inactive status for a period up to 5 years. During this time, a PI may request re-activation of the protocol without submitting a new protocol (unless there are substantive changes from the original protocol). After a protocol has been on inactive status for 5 years, it will be discontinued.

Serious Adverse Events

The PI must immediately report to his/her institution's IRB and the CBeIRB all adverse events within 48 hours, even if there is no obvious causal relationship between the study activities and the event. The institution's IRB, in turn, is responsible for reporting all adverse events to the institution's management, to DOE/HQ, and to any other federal agency funding the research protocol, and notifying the CBeIRB of the report. When required, the responsibility for reporting the serious adverse event to the Office of Human Research Protections (OHRP), devising a remediation plan, and for all related follow-up activities will be managed by the CBeIRB in conjunction with the institutional and site IRBs for each research project.

CHAPTER 7: MONITORING

Research Conduct

During the course of the research, the PI must comply with all CBeIRB decisions, directives, conditions, and the responsibilities described in these Guidelines. The CBeIRB may contact subjects directly or monitor the research to evaluate the PI's conduct and compliance with requirements.

Noncompliance/Violations/Complaints

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

The CBeIRB Chair must report the following to the appropriate institutional official and to DOE/HQ:

- Any serious or continuing noncompliance with the regulations or requirements of the CBeIRB.
- Any suspension or termination of CBeIRB approval for research.

Unanticipated Problems and Adverse Events

When unanticipated problems or adverse events occur in the research process, they must be systematically evaluated, corrected, and possibly reported. The phrase *unanticipated problems* involving risks to subjects or others is found but not defined in 45 CFR 46. OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

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

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

(3) 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.

Likewise, the term *adverse event* is found but not defined in 45CFR 46. In OHRP guidance, the term *adverse event* in general is used very broadly and includes any event meeting the following definition: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subjects participation in the research, whether or not considered related to the subjects participation in the research. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

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

Any individual noting a deviation from an approved protocol should report the deviation or concern to the CBeIRB. The CBeIRB will then review the protocol and relevant documentation and assess the deviation according to two main criteria:

- Potential or actual harm to the subject.
- Potential or actual effect on the integrity of the study data.

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

The CBeIRB will also determine whether further corrective action is warranted:

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

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

Suspension/Termination Procedure

The CBeIRB has both the authority and the responsibility to suspend or terminate any research involving human subjects that is not being conducted in accordance with CBeIRB requirements or that has been associated with any serious adverse event. Any such suspension or termination of approval will be communicated promptly to the PI and shall include a statement of the reasons for the suspension. The CBeIRB Chair will also notify the Designated Institutional Representative, DOE/HQ, and DHHS/OHRP.

CHAPTER 8: MEETINGS

Scheduled Meetings

At least one convened meetings of the Board shall occur within each 12-month period. Meetings may be held more frequently as necessary to assure that the Board meets its responsibilities in accordance with 45 CFR 46.

Agenda

The CBeIRB Administrator will prepare a preliminary agenda for each meeting. After approval by the CBeIRB Chair, the Administrator distributes the agenda to all members at least 10 days prior to the meeting along with meeting materials to be reviewed prior to the meeting. A final Agenda is distributed at each meeting.

Minutes

The CBeIRB Administrator or Secretary records and transcribes the minutes of each convened meeting of the CBeIRB (for required content of minutes, see Chapter 9: Record Keeping). After review and approval by the Chair, CBeIRB, the Administrator will distribute meeting minutes to the membership for review and comment prior to the next full Board meeting. Final review by the Board, including modifications if needed, will occur at the beginning of the next full Board meeting. Any corrections, modifications, or additions to the minutes will be reported in the next set of meeting minutes.

Copies of the minutes will also be sent to the DOE Oak Ridge Operations Office, Human Subjects Representative and to the Designated Institutional Representatives of sponsoring institutions (ORAU, DOE/HSS and DOE/SC).

Quorum and Voting

A quorum is defined as a majority of CBeIRB voting members, including at least one non-scientist member. When a proposal will be reviewed at a meeting, the Administrator assures a quorum is present. Should the quorum fail during a meeting (e.g., loss of a majority through recusal of members with conflicting interests or early departures, or absence of a non-scientist member), the CBeIRB may not take officially binding further actions or votes unless the quorum can be restored.

All voting is conducted in closed session, and voting privileges shall be limited to CBeIRB voting members present at the meeting. Proxy votes are not accepted. Board votes are recorded by the Administrator; a majority vote is required for any CBeIRB determination.

No member may participate in the CBeIRB vote or review of any protocol in which the member has a real or perceived vested interest or conflicting interest, except to provide information requested by the CBeIRB. CBeIRB members shall absent themselves from the meeting room when the CBeIRB reviews research in which they have a conflicting interest, and such shall be noted in the CBeIRB meeting minutes.

A CBeIRB member must abstain from voting to approve a protocol if she or he has a conflict of interest. Such action will be noted in the meeting minutes.

Alternate members

Alternate members may be appointed for each of the voting members representing DOE beryllium sites. Alternate members are nominated by the Chair of the site IRB to serve in the absence of that site's regular IRB representative. Appointment shall be made in writing by the President, ORAU. If both the representative voting member and the alternate are present at a meeting, both can participate in discussions, but the alternate may not vote nor count toward a quorum. If the voting member is absent and the alternate is present, the alternate may vote.

CHAPTER 9: RECORD KEEPING

Records Retention and Access

All records related to the participating institutions' human subjects research shall be archived and stored. The minimum retention period shall be as long as required by law and DOE records retention schedules. These records shall be accessible for inspection, audit, and copying by authorized representatives of the funding Agency or any involved IRBs at reasonable times and in a reasonable manner.

CBeIRB Records

All official CBeIRB records are stored in the CBeIRB Administrator's office in locked file cabinets for a minimum of three years after completion of the study, consistent with the requirements of 45 CFR 46.115. After that time, all CBeIRB records will be archived and stored in a secured area for the period specified by DOE record retention schedules.

Protocol Records

The CBeIRB Administrator assigns each protocol a unique, sequential number that indicates the fiscal year and order of receipt. Official CBeIRB records for each protocol include the following:

- All documentation reviewed by the CBeIRB.
- All correspondence related to the protocol.
- A list of all telephonic communication related to the protocol with a brief summary of the content of each phone call.
- Copies of any press releases of the protocol that are initiated by the PI
- Notes from protocol review sessions including reviewer written comments.
- Approved consent forms, which must include the initial approval date, the current approval date, the expiration date, and the corresponding protocol number. (Note: The PI retains all signed consent forms.)
- All other documents specifically required by the CBeIRB relating to the protocol (e.g., any subject recruitment material, questionnaires, a list of any published articles, or documents required by any special conditions established by the DOE).

Meeting Minutes

Minutes (45 CFR 46 (a)(2)) of CBeIRB meetings shall be taken in sufficient detail to show the following:

- Attendance, including members, invited experts, and any guests present; members absent, as well as late arrivals or early departures by voting members and/or their alternates.
- Actions taken by the CBeIRB (including listings of exempt and expedited reviews) and annual reports.

- The vote on these actions, including the number of members voting for, against, and abstaining.
- The basis for requiring changes or disapproval of proposed protocols.
- A written summary of the discussion of controversial issues and the Board's action.
- Reports of unanticipated or adverse events and the action taken by the Board.

Training Records

Members shall keep documentation of training, or records of completion of training, as required by the Board. Proof of required training must be furnished to the IRB administrator who will maintain a record of training for each Board member.

PI Records

The PI must retain all research-related records that originate with the PI or the research team for the length of time as required by law, terms of DOE contract or grant, or as stated in the Federal Register.

Administrator Records

The IRB Administrator maintains the following records in compliance with 45 CFR 46.115:

- As required by 45 CFR 46.103(b) (3), a current Membership List lists members and their areas of expertise.
- Board members' CVs, at time of appointment and reappointment to the Board.
- Written procedures for the CBeIRB and investigators.
- Copies of all research proposals reviewed and consent forms approved.
- Minutes of CBeIRB meetings.
- Records of continuing review activities.
- Copies of correspondence between the CBeIRB and the investigators and their local site and institutional IRBs.
- Reports of any Adverse Event/Effects

CHAPTER 10: REFERENCES

These programs were established to address adverse health effects resulting from occupational Be exposure among workers in DOE and DOE-contractor facilities are

- The final rule to establish a Chronic Beryllium Disease Prevention Program; Worker Health and safety Program; Final Rule published in February 2006, 10 CFR Parts 850 and 851.

- The Energy Employees Occupational Illness Compensation Program Act of 2000.

Authority for these Standing Operating Procedures is contained in the following documents:

- 10 CFR 745, "Protection of Human Subjects,"
- Department of Energy Policy DOE P 443.1A, "Protection of Human Subjects,"
- Department of Energy Order DOE O 443.1A, "Protection of Human Subjects,"
- ORAU Policy GP-225 "Protection of Human Participants in Research"
- DOE Human Subjects Handbook

CHAPTER 11: DEFINITIONS

Adverse event - An undesirable effect to the subject (physical, nonphysical, psychological, social, financial), that occurs to a research subject as a result of participation in a research protocol from the time of a subject's consent until the subject's final study follow-up is completed. Adverse events may be anticipated or unanticipated.

Atomic Energy Act of 1954 – Passed to promote the peaceful uses of nuclear energy through private enterprise and to implement President Eisenhower's Atoms for Peace Program. The Act allowed the Atomic Energy Commission to license private companies to use nuclear materials and build and operate nuclear power plants. This act amended the Atomic Energy Act of 1946, which had placed complete power of atomic energy development in the hands of the Atomic Energy Commission.

Conditional Approval – A protocol the Chair, CBeIRB will approve contingent upon the PI successfully addressing a set of specified concerns identified during any type of protocol review.

Conflict of Interest – Any affiliation, personal, professional, or financial connection with the institution or person submitting a protocol that might be construed as creating a conflict.

DOE/HQ - Department of Energy Headquarters

Engaged in Human Subjects Research – Awardee institutions are automatically considered to be "engaged" in human subject research whenever they receive a direct HHS award 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.

Federal-wide Assurance - The Federal Policy (Common Rule) for the protection of human subjects requires that each institute "engaged" in Federally-supported human research file an "Assurance" of protection for human subjects. The Assurance formalizes the institution's commitment to protect human subjects. The requirement to file an Assurance includes both "awardee" and collaborating "performance site" institutions.

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 Subject - A living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

> *Intervention* includes both physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
>
> *Interaction* includes communication or interpersonal contact between investigator and subject.
>
> *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

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

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

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

Ongoing Study / Project – A study/project previously reviewed and approved by the CBeIRB.

Principal Investigator (PI) - The scientist or other individual designated by his or her site 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 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 investigator or associated with the information) in order for collection of the information to constitute research involving human subjects.

Proposal Review Package – The minimal information required by the CBeIRB from the PI in order to conduct a review of proposed research. This package includes the following:

- A completed Review Request (Application) form signed by the PI and his or her Director.
- A 1-2 page abstract of the proposed research, (including a description of risks and benefits).
- A complete research proposal is required if the Be research is a component of a broader study, not just the Be component of the protocol. This documentation should include provisions for the protection of human subjects in accordance with all applicable laws and regulations, and any related paperwork (e.g., an activity-specific Standard Operating Procedure, manufacturer's specification sheets, safety reports, etc.).
- A proposed Informed Consent form that includes all required elements.
- Any proposed advertisement or recruitment materials.
- Copies of approvals from any collaborating institutions' IRBs.

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.

Serious Adverse Event - Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

(1) results in death;
(2) is life-threatening (places the subject at immediate risk of death from the event as it occurred);
(3) requires inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or

(6) 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).

Unanticipated 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:

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