CENTRAL BERYLLIUM INSTITUTIONAL REVIEW BOARD (CBeIRB)

STANDARD OPERATING POLICY AND PROCEDURES

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CHAPTER 1 PURPOSE, BACKGROUND, AND SCOPE

Purpose

The purpose of this manual is to document the operating procedures of the 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 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.[1]

Background

The CBeIRB was established in 2001 and is funded by the DOE Office of Science (SC), and the Office of Environment, Safety and Health (EH). 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 443.1, Protection of Human Subjects where applicable. 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 policy and procedures described herein apply to all new research meeting the CBeIRB review criteria. **Ongoing Be-related research initiated prior to the development of this document will be reviewed following the procedures described in the Addendum.** Specifically, ongoing programs that are subject to review by the CBeIRB are the Former Beryllium Workers Medical Surveillance Program (see attached), the beryllium screening component of the Former Workers Program (see attached), and any site or off-site human subjects research activities related to beryllium exposure and medical testing for beryllium sensitization or disease.

When there is an IRB at a DOE site or at other participating organizations, their input will be solicited by the CBeIRB prior to CBeIRB review. As questions or uncertainties arise regarding the applicability of human subjects protection regulations, the final resolution is determined by SC, which holds this responsibility within the Department.[2]

[1] ORAU Policy GP-225 "Protection of Human Participants in Research."

Questions regarding this process may be addressed to DOE's Human Subjects Program Manager. The DOE Human Subjects program website can be found at: http://www.science.doe.gov/ober/humsubj/index.html.

Specifically excluded from this policy are activities related to DOE site-specific medical surveillance of its workers under the DOE Chronic Beryllium Disease Prevention Program Final Rule, 10 CFR 850, provided the DOE site is using the Informed Consent Form included in Appendix A to Part 850 without revisions. However, if the Informed Consent Form included in Appendix A of Part 850 as written is not used, CBeIRB review of any substitute to be used in place of that consent form is strongly advised. 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. 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 employees or ex-employees.

Scope

The CBeIRB is responsible to DOE/SC for providing a high level of expertise and diverse, experienced members to address Be-related human subjects protection issues. It provides DOE, DOE contractors, and any other organization(s) engaged in research on Be exposure, testing, or disease funded by DOE and/or involving the DOE workforce, active or retired, with a thorough and consistent review that is essential to protection of the volunteer subjects in these programs.

[(2)] In a memo dated January 20, 1998, (http://www.science.doe.gov/ober/humsubj/hspolicy.html) the Secretary of Energy assigned the Office of Science responsibility "for making final decisions as to what constitutes DOE-related human subject research and how human research subject protection must be implemented," Secretary of Energy memo, "Update on Departmental Policy for the Protection of Human Subjects in Research." This manual applies to all activities of the CBeIRB

CHAPTER 2 INTRODUCTION

History

The Atomic Energy Act of 1954 was enacted to promote the peaceful uses of nuclear energy. Beryllium exposures to DOE employees and the employees of DOE contractors have occurred as a result of the use of beryllium (Be) in weapons production and research. The number of persons detected with chronic beryllium disease across the DOE complex has been increasing because of DOE's emphasis on testing the retired workforce and the new requirement to offer testing to the current workforce. This has sparked an increased awareness of and concern about this serious occupational illness and has resulted in DOE-wide beryllium sensitization 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.

Rationale for a Central BeIRB

DOE is obligated to ensure that studies related to Be exposure and medical testing to understand the pathogenesis of CBD are conducted in accordance with defined prevailing ethical standards. All research involves both risks and benefits. The risks may include possible direct harm from research procedures and indirect harm resulting from consequences to the individual of having the information, such as employability and insurability, or the release of information such as a loss of privacy. Likewise, benefits may accrue, such as more specific medical treatment or financial remuneration. Heightened sensitivity to the information given and support offered to workers before participation in Be studies is essential to allow the individual worker to make informed choices about such participation. Because these issues must be properly addressed in a research endeavor, Institutional Review Board (IRB) review and approval of the Be study protocol is required before any workers can be invited to participate in these activities.

The requirement for IRB approval poses a problem at some DOE sites that have no IRB but have workers who were or may have been exposed to Be. Even if the DOE site or DOE-funded grantee has access to an IRB, that IRB may have insufficient knowledge of dealing with beryllium-related issues to evaluate the adequacy of protection of human subjects. The CBeIRB will provide expertise and consistency in addressing human subjects protection issues across the complex by communicating with and educating existing IRBs and filling the void at those site not having an IRB.

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" (the *Belmont Report*). 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 institutions) 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.

In addition, the requirements set forth by the Common Rule in Title 45, Part 46 of the Code of Federal Regulations (45 CFR 46) and in 10 CFR 745 will be met for all applicable research regardless of the funding source. The reporting information will be as required by the funding source, and by DHHS and DOE and by other funding sources as applicable.

CHAPTER 3 AUTHORITIES AND RESPONSIBILITIES

ORAU

ORAU has established and shall operate and maintain the CBeIRB for DOE/SC and EH in accordance with 45 CFR 46 and 10 CFR 745. The Board shall have the responsibility and authority to review, approve, give conditional approval, withhold approval, disapprove, or request changes in any of the participating institutions' Be-related research activities involving human subjects. The President of ORAU has the responsibility of providing the support and resources necessary to ensure the effective operation of the CBeIRB, appointing qualified members to the board, and overseeing the overall quality and efficiency of the board's performance. ORAU has provided and will continue to 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 responsibilities under the DHHS assurance.

Institutional Officer

The President, ORAU, is the Institutional Officer responsible for the CBeIRB's FWA with DHHS.

Designated ORAU Representative

The President of ORAU may appoint an individual to represent him or her 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 member of the CBeIRB.

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.
- Develops and 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 by DHHS to maintain DHHS certification as an IRB Administrator.
- Serves as a non-voting member of the Board.

The IRB Administrator shall maintain the following records in compliance with 45 CFR Part 46, Section 115:

- A current roster of CBeIRB members as required by 45 CFR 46.103(b)(3).
- Board members' CVs, updated at least on appointment and reappointment to the Board.
- Delegation of authority.
- 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

CBeIRB Secretary

The CBeIRB Secretary of Record is responsible for recording the minutes of CBeIRB meetings and preparing the official meeting record, maintaining CBeIRB records and files, and assisting the CBeIRB Administrator and CBeIRB Chair as required.

CBeIRB Chair

The CBeIRB Chair is appointed by the President of ORAU. The Chair is responsible for ensuring that the Board carries out its responsibilities. The Chair also has the following responsibilities:

- Determines the type of review required (Full Board, Expedited, Exempt).
- Conducts expedited reviews or appoints voting members of the Board to expedited review subcommittees.

Site & Research Institution Officials

The CBeIRB expects that the managements of participating institutions will encourage and promote constructive communication among the research administrators, department/program heads, principal investigators, the Board, other institutional officials, human subjects, and their representatives in order to maintain a high level of awareness regarding the safeguarding of the rights and welfare of the subjects involved in Be-related research.

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 and any requirements of 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 risks to such subjects 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, and 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 forward 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 training in Human Subjects Protection.

CHAPTER 4 CBeIRB STRUCTURE

Membership

10 CFR 46 provides that 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. The CBeIRB members must be sufficiently qualified in expertise, experience, and diversity of background, including diversity in racial and cultural heritage and sensitivity to issues such as community attitudes, to promote respect for its advice and counseling in safeguarding the rights and welfare of human subjects involved in Be-related research. CBeIRB members must be able to ascertain the acceptability of proposed Be-related research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.

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 are 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 includes representatives from all stakeholders in the Be research community. To capitalize on the experience of IRBs located at DOE sites with a history of Be research, one member from each of three site IRBs serves a 2-year renewable term on the CBeIRB. The IRBs of Pacific Northwest National Laboratory, Lawrence Livermore National Laboratory, and Rocky Flats Environmental Technology Site currently provide one member each to serve as a site IRB representative on the CBeIRB as voting members. The Chairs of each of the three site IRBs may designate one site IRB member to serve as an alternate member in the absence of the site representative. If the voting member for whom the alternate is eligible to substitute is absent, the alternate may be seated, counted in the quorum, and vote

Selection and Appointment of Members

Voting Board members and all non-voting representatives to the Board are responsible for nominating (in writing) persons for membership to the Board. Appointments to the Board shall be made by the ORAU President with the approval of a simple majority of all the voting members and non-voting representatives. Voting members other than the three site representatives shall be appointed to serve for one renewable term of 3 years. Term renewal is at the discretion of the full Board. Appointments shall be made in writing by the President, ORAU. New members shall sign a confidentiality statement and a statement promising to acknowledge conflict of interest as it occurs.

The Board shall nominate in writing an active or former member to serve as its Chair for one renewable 3-year term; no one shall serve more than 2 consecutive terms as Chair. All voting members of the Board will be polled to vote on the Board's nominations for Chair. Appointment shall be made in writing by the President, ORAU.

The Board shall nominate an active or former member to serve as the Vice-Chair for one renewable 3-year term; no one shall serve more than 2 consecutive terms as Vice-Chair. All voting members of the Board will be polled to vote on the Board's nomination. Appointment shall be made in writing by the President, ORAU. The Vice-Chair has the authority to act for the Chair in his/her absence.

The Board may nominate any member to serve a 1-year ex-officio (non-voting) term. Former members are eligible for reappointment after a hiatus of 3 years. No Board member may serve in a voting capacity more than 6 consecutive years.

The responsibilities of the Board Secretary (non-voting) shall be assigned by ORAU; the Secretary shall serve as the Secretary of Record of the CBeIRB.

Resignation/Termination of Members

Members may resign from the CBeIRB at any time, but completing existing terms or remain active until a replacement is designated is encouraged.

Termination by the ORAU President 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, or failure to complete work as assigned or requested by the Chair.

A recommendation to the President of ORAU for termination of a member from the Board requires approval of two-thirds of all voting members of the Board and the Designated Institutional Representative(s).

Member Training

Members are required to successfully complete the Human Subjects' training developed for DOE by the Center for Information Technology Integration (CITI) or a recognized equivalent, e.g., NCI HS program, within three months of appointment to the Board. They also must complete a related continuing education module each year of Board service thereafter. 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. Alternate training programs may be acceptable in lieu of the CITI program if approved by the Chair.

In addition, time is allocated on the agenda during each meeting for member education and to address current issues and pending changes in regulations. The CBeIRB Administrator and Chair also use this time to disseminate information obtained from national meetings and conferences attended throughout 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 other agencies or institutions be reviewed and approved by the CBeIRB prior to the collection of data.

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 subjects protection regulations to studies that use

human subjects, the final resolution is made by the DOE Human Subjects Protection Program Manager.

To ensure the privacy of workers or others included in Be studies, to maintain the independence of PI's institutions to conduct these studies at DOE sites, to ensure local input in a timely fashion, and to respect the independent obligations of DOE contractors, whether by contract or law, SC established the following procedures concerning review of Be study protocols that include DOE and DOE-contractor workers in the study population. As was previously described, because some studies were ongoing when the CBeIRB was established, the procedures are divided into two parts: 1) initial/continuing review of new protocols (described in the following section) and 2) initial/continuing review of ongoing protocols (described in the Addendum). In all cases, 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 DOE or DOE-contractor workers are included in the study population.

Initial Review of New Studies by CBeIRB

The DOE/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. Responsibility for this notification shall be assigned by the PI's institution to an employee of that institution. 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.

PIs may recommend to the CBeIRB the level of review they consider appropriate, but only the CBeIRB Administrator or 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 PIs by the CBeIRB Administrator.

In the absence of a timely scheduled meeting of the CBeIRB, the CBeIRB Chair or his/or designee(s) will review protocols requiring full Board review for interim approval and notify the PI of the outcome within five working days of the receipt of the protocol from the PI. Interim approval allows planning and other preliminary work on the study to proceed, but data collection and subject contact, interviews, etc., must await full board review and approval.

When the CBeIRB's approval of a protocol is final, the PI provides clean copies of all revised documents as approved to the CBeIRB Administrator. The CBeIRB Administrator returns them to the PI, stamped as applicable to show the date and duration of the CBeIRB's approval, keeping a copy of each for the files.

All proposals eligible for initial review by the CBeIRB must have the Board's approval before they may be implemented.

Continuation Review

As previously described, the federal regulations at 45CFR46.109 (e) require 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. 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 on the Continuing Review Application Form (Attachment G-2)

Protocols Requiring Initial or Continuing Reviews by Multiple IRBs

It must be recognized that DOE-related beryllium research may be subject to review by both the site and institutional IRB of the principal investigator before submission to the CBeIRB. This poses potential problems for the PI in terms of scheduling and coordinating initial and continuing reviews with the different boards, resolving conflicting directives stemming from multiple reviews of the same protocol, determining priorities for reporting adverse events and protocol amendments to the different boards, and similar activities.

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 (e.g., PI, PI's institution's IRB, site/local IRB).

For new proposals these discussions will be initiated by the CBeIRB when notice of the proposed Be-related study/project is received from the PI or from DOE/SC. 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 each new proposal, the CBeIRB will work with the site IRB where there is one to explore the feasibility of developing a written agreement (e.g., Cooperative Agreement, Memorandum of Understanding) whereby the responsibilities for IRB review may be coordinated. Such an agreement shall be drafted jointly for review and approval by the IRBs' respective Institutional Officers. Where feasible a similar agreement will be developed between the CBeIRB and the PI's institutional IRB and any other IRBs with authority over the project. These agreements will be protocol/project-specific and will specify the procedures for initial and continuing review and for review of modifications and adverse event reports relating to the corresponding protocol/project. Within this framework there is the potential for more than one model.

The CBeIRB will make similar efforts to coordinate continuing reviews of projects that were ongoing before it was established (e.g., Former Worker Medical Surveillance projects) with the site, PI's institutions and any other IRBs responsible for the individual projects.The site IRB may defer to the CBeIRB the responsibility for continuing review of the beryllium screening component of the overall project only or of the overall project including the Be component.

Levels of Review

Federal regulations at 45CFR46 allow 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 of the CBeIRB reviews all protocols submitted for review to determine the appropriate level of review required considering any recommendations made by the PI, local/site or other institutional IRBs.

Note: The CBeIRB makes the **final determination** of the type of review the protocol warrants.

Exempt Review

Certain low-risk research activities are exempt from rigorous IRB review; however, the CBeIRB Chair must conduct a preliminary review to determine whether the research meets the criteria for exemption (see Attachment C). Regardless of the determination of the local/site institutional IRBs, the final determination shall be made by the CBeIRB.

Note: The CBeIRB Chair (in consultation with other board members if appropriate) shall have the authority to make the determination as to what level of review is required. 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, 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 to achieve approval, or refer it to the full Board. However, proposed research cannot be disapproved under expedited review.

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 (see Attachment D)

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 a single board member 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. A vote of the members to approve the protocol shall be taken by a show of hands and recorded in the meeting minutes.

Full Board Review

All other human subjects 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.

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.

Research protocols scheduled for review shall be distributed to all members of the Board at least 10 working days prior to the meeting.

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

All initial, continuation reviews, and protocol amendments requiring full board review shall be conducted at convened meetings and at timely intervals.

If warranted, CBeIRB meetings may be convened and conducted via telephone conference call that may 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 controverted issues).

A Board member whose concerns are primarily in nonscientific areas must be present at the convened meeting before the Board can conduct its review of research.

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.

For a research protocol to be approved it must receive the approval of the majority of the eligible voting members present at the convened meeting.

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.

In cases where research activities were initially approved under expedited procedures and subsequently reviewed by non-expedited procedures, the decisions reached at the convened meeting shall supersede any decisions made through the expedited review.

Primary/Secondary Reviewers

The CBeIRB uses the Primary/Secondary Reviewer System for all protocols requiring full board review. Both reviewers shall do 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 a protocol summary (of sufficient detail to make the determinations required under DHHS regulations at 45 CFR 46.111), the proposed informed consent document, and any advertising material. Primary and secondary reviews should point out and discuss all the relevant issues, but should not document approval or disapproval of the research; they should only make a 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 that pertinent laws and regulations are observed. 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 ***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 subjects protection methodologies, sampling plan/statistical design, data management and data security/ confidentiality plan, dissemination and notification plan, recruiting materials).

- Any copies of supporting technical/peer reviews, internal or external, of the protocol.
- Current protocol or project handbook, if appropriate (to include all current local site and CBeIRB-approved consent forms, fact sheets, data collection instruments)
- Documentation of compliance with Privacy Provisions of HIPAA, where appropriate (copies of approved authorizations from participating covered entities)
- Informed Consent Document and Procedure

Informed Consent

Investigators shall include with the protocol, a draft of all applicable informed consent documents that address all the elements of informed consent as prescribed in 45 CFR 46, section 116, and other elements recommended by the CBeIRB to be routinely included in a consent form (See also: Attachment E). Principal Investigators are responsible for ensuring that legally effective informed consent shall:

- Be obtained using a consent form that has been reviewed and approved by the local site and CBeIRB within the previous 12 months or less as previously prescribed by the IRB.
- 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.
- 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.

Unless otherwise authorized by the Board, Principal Investigators at a minimum shall provide the following to each subject in the informed consent document:

- The names, affiliation, addresses of the principal and any co-investigator(s), the sponsor (funding source), and location at which the research will be conducted.
- 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 as they involve human subjects, and identification of any procedures that are experimental.

- A description of any benefits to the subject or to others that may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be available.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and identifying the individuals (by title), institutions, and/or agencies that may routinely use or access the records.
- For research involving more than minimal risk, explanations as to whether any compensation or medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- A statement describing how, where, for how long, and in what form the data will be used, stored and maintained, and how and to whom the results of the research will be reported to assure the privacy of the subject and the confidentiality of the subject's personally sensitive information.
- Immediate and direct access at the time of consent to an individual capable of answering any questions related to the study.
- An explanation of whom to contact for answers to pertinent questions about (a) any research-related injury to the subject, and (b) the research and research subjects rights and responsibilities; this shall include identification of "the Chair, CBeIRB" as an alternate source of information about subjects' rights.
- A statement that participation is voluntary, and refusal to participate or discontinue participation at any time will not result in any penalty or loss of benefits to which the subject is otherwise entitled.
- A statement of the action, if any, to be taken by the subject if he/she decides to withdraw from the research before its completion, and of the disposition of the subject's data compiled up to the time of withdrawal.
- A copy of the consent form.

When required by the Board, the Principal Investigator also shall provide one or more of the following additional elements of information to each subject:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable.
- A statement that the Principal Investigator may decide to withdraw the subject from the research, and the sponsor might terminate funding, without notification.
- Anticipated circumstances under which the subject's participation may be terminated by the research investigator without regard to the subject's consent.
- Any additional costs to the subject 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 which may relate to the subject's willingness to continue participation will be provided to the subject.
- The approximate number of subjects involved in the study.

The CBeIRB may permit the Principal Investigator to use a consent form that is either:

- A written consent document that embodies the elements of informed consent required by 45 CFR 46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the research investigator or other person obtaining the consent shall document by signing that either the subject or the representative has been given adequate opportunity to read or to listen to a recording of the form before signing it.
- A "short form" written consent document stating that the elements of informed consent required by 45 CFR 46.116 have been presented orally to the subject or the subject's legally authorized representative. When the "short form" is used, PI shall ensure that:

    - The written summary of what is to be said to the subject or the representative receives the prior approval of the Board.
    - A witness is present at the oral presentation.
    - The subject or the representative signs the short form; the witness signs both the short form and a copy of the written summary of the oral presentation.
    - The person obtaining consent signs a copy of the summary.
    - The names of all signatories also shall be printed or typed, with the date and time.
    - A copy of both the short form and summary is given to the subject or the representative.

At the request of the PI, the requirement to obtain a signed consent form may be waived for some or all subjects if the Board determines that:

- 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.

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 research involves no more than minimal risk to the subjects.
- 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** as is (protocol is approved as submitted).
- **Approve with conditions** (review package requires modifications or PI must furnish additional information).
- **Table** (protocol/review package needs major work 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) Approve

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 (e.g., the CBeIRB may require third-party observation of the consent process).

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 and provides documentation to the CBeIRB within a reasonable time as set forth by the Board (21 working days).
3. CBeIRB verifies (by the Chair and the primary/secondary reviewer) that conditions are met .

Note: If verification cannot be made, the proposal cannot be approved.

Table

When a protocol is submitted for review 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 this documentation is received and reviewed for approval by the full Board at its next scheduled meeting.

Disapproval

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 proposals that it did not approve.

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 for the Chair's signature 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.

Note: Research that has been approved by the CBeIRB may be subject to further review and approval by other institutional officials; however**, no individual or committee at the participating institutions may approve or conduct a research project that has not been approved by the CBeIRB.**

Documentation

After CBeIRB approval and before beginning a research protocol, the PI must be able to show that the proposed research and consent documents have been reviewed and approved by the CBeIRB and all subjects are fully informed, and that their consent has been documented in signed consent forms (unless the signature requirement was specifically waived by the CBeIRB). The Chair will determine the level of review required prior to implementation of any amendments (see Request for Modification of Amendment).

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 no less than once annually. 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. In conducting cooperative 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.,10 CFR 745 §101(h)).

CHAPTER 6 POST-APPROVAL REVIEW OF NEW PROTOCOLS

Serious Adverse Events

The PI must immediately report to his/her institution's IRB and the CBeIRB all serious 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. 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 conducted in accordance with the multi-site review agreements negotiated by the CBeIRB and institutional and site IRBs for each research project.

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 the review of new protocols and continuation 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. The level of review required will be determined by the Chair of the CBeIRB. No changes to an approved protocol shall be implemented without their approval by 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 of 5 years. During this time, a PI may request re-activation of the protocol without submitting a new protocol (unless there are significant changes in the protocol). After a protocol has been on inactive status for 5 years, it is then discontinued.

CHAPTER 7 MONITORING

Research Conduct

During the course of the research, the PI must comply with all CBeIRB decisions and conditions and the responsibilities described in these Guidelines.

Note: 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. Allegations that are substantiated will be forwarded to the CBeIRB Chair for appropriate action as outlined below.

The CBeIRB Chair must promptly 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.

Deviation from Approved Protocol

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 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 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, a memo will be sent from the CBeIRB Chair to the PI's supervisor.

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 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 CBeIRB Chair must also notify the institution's director, DOE/HQ, and DHHS/OHRP.

Self-Assessment

The CBeIRB shall periodically conduct self-assessments to ensure compliance with requirements and to evaluate the effectiveness/efficiency/suitability of procedures. In addition, the CBeIRB is subject to audit by DHHS/OHRP.

CHAPTER 8: MEETINGS

Scheduled Meetings

At least two convened meetings of the Board shall occur within a 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. A PI may request, or be requested, to attend a meeting in person or by teleconference call to discuss his/her protocol; however, no PI may be present during a vote on his/her proposal.

Agendas

The CBeIRB Administrator prepares a preliminary agenda for each meeting, and after approval by the CBeIRB Chair, distributes it to all members at least one week prior to the meeting along with meeting materials to be reviewed prior to the meeting. A final Agenda is distributed at each meeting for approval by the membership before proceeding.

Minutes

The CBeIRB Secretary records the minutes of each convened meeting of the CBeIRB (see "Record Keeping" for required content of minutes). Upon securing approval of the CBeIRB Chair, the Administrator will distribute meeting minutes to the membership for review and comment as soon as possible after a meeting. Minutes are submitted to the Board for approval at the next full Board meeting.

The officers of the participating institutions shall be kept informed of Board activities through distribution of final copies of Board's meeting minutes that are distributed to the institutions' designated representatives to the Board.

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 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 members present at the meeting. Proxy votes are not accepted. Member votes are recorded by the Administrator via a show of hands, and 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 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 may abstain from voting to approve a protocol if she or he has a conflict of interest.

The rules contained in the current edition of ***Robert's Rules of Order Newly Revised*** shall govern meetings in all cases to which they are applicable and in which they are not inconsistent with any special rules of order the Board may adopt.

Alternate members

Alternate members may be appointed for each of the voting members (3) representing the DOE's Be sites. Alternate members are nominated by the Chair of the site IRB represented on the Board to serve in the absence of the IRB member representative. Appointment shall be made in writing by the ORAU President. 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 can vote.

CHAPTER 9 RECORD KEEPING

Records Retention and Access

All records related to the participating institutions' human subjects research shall be archived and stored. They shall be retained for at least as long as required by law and DOE records retention schedules. These records shall be accessible for inspection and copying by authorized representatives of the funding Department or Agency 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. After that time, all CBeIRB records will be archived and stored in a secured area.

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.
- Copies of any press releases of the protocol that are initiated by the PI
- Notes from protocol review sessions including Reviewers 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, etc.).

Meeting Minutes

Minutes of CBeIRB meetings shall be taken in sufficient detail to show the following:

- Attendance, including members (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 in or disapproval of research.
- A written summary of the discussion of controverted issues and their resolution.
- Reports of unanticipated problems and adverse effects.

Minutes are filed chronologically. Non-protocol-specific correspondence is kept in a separate "Business" file.

Minutes are distributed to voting members for review as soon as possible after a meeting. Any corrections/comments to the minutes are noted in the minutes of

the next meeting, and a vote is taken to approve the minutes. Copies of the minutes also are sent to the DOE Oak Ridge Operations Office Human Subjects Representative and to the Designated Representatives of sponsoring institutions (ORAU, DOE/EH and DOE/SC).

Training Records

Members shall keep documentation of training, or records of completion of training, as required by the Board.

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.

CHAPTER 10 REFERENCES

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

- The Former Beryllium Workers Medical Surveillance Program announced in December 1998, in response to the requirements of 42 USC Sec, 7274I. "Program to Monitor Department of Energy Workers Exposed to Hazardous and Radioactive Substances,"
- The final rule to establish a Chronic Beryllium Disease Prevention Program (CBDPP), 10 CFR 850, published in December 1999,
- The Energy Employees Occupational Illness Compensation Program Act of 2000, signed into law in October 2000, and became effective July 31, 2001, providing employees in DOE facilities who suffer from CBD monetary compensation for the disability and medical expenses associated with the disease.

Authority for these procedures is contained in the following documents:

- 10 CFR 745, "Protection of Human Subjects,"
- Department of Energy Policy DOE P 443.1, "Protection of Human Subjects,"
- Department of Energy Order DOE O 443.1, "Protection of Human Subjects,"

- Secretary of Energy Memo "Update on Departmental Policy for the Protection of Human Subjects in Research" (01/20/1998),
- Access Handbook, Conducting Health Studies at Department of Energy Sites

CHAPTER 11 DEFINITIONS

Adverse event - An undesirable effect to the subject (physical, nonphysical, psychological, social, financial), whether expected or unexpected, that occurs from the time a subject consents until the subject's final study follow-up is completed.

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 CBeIRB Chair or her/his designee will approve contingent upon the PI addressing a set of specified issues.

Conflict of Interest – Any affiliation, personal, 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 Subject 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.

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:

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

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.

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 - 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 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 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 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 (see Attachment E, "Elements of Informed Consent").
- Any proposed advertisement or recruitment material for human volunteers.
- Copies of approvals by the PIs and 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.

ATTACHMENTS

Attachment A

Former Beryllium Workers Medical Surveillance Program Sites

The Former Beryllium Worker Medical Surveillance Program is designed to assess the health impacts of DOE operations on former employees thought to have worked with beryllium. Currently, the program is carried out by the Oak Ridge Institute for Science and Education (ORISE). ORISE offers medical screening examinations and diagnostic evaluations to individuals with positive screening results.

AL:	Kansas City Plant, Pantex Plant, Sandia National Laboratory, Burlington Plant
CH:	Argonne National Laboratory (East and West), Fermi National Laboratory, Brookhaven National Laboratory
OAK:	Lawrence Livermore National Laboratory, Stanford Linear Accelerator Laboratory
OH:	Fernald, Mound
OR:	Oak Ridge National Laboratory, Y-12 Plant
RF:	Rocky Flats Site
SNRO:	Knolls Atomic Power Laboratory

Former Worker Program Sites

This program identifies former workers who might be at risk of adverse health effects as a result of their DOE employment at the sites listed below. Targeted medical screening is offered based on the workers' highest occupational exposures, which can include any or all of the following: beryllium, asbestos, radiation, cadmium, chromium, silica, welding fumes, lead, solvents, mercury, and noise.

AL:	Development of a Screening Program for Former Los Alamos National Laboratory Workers (conducted by Johns Hopkins University)
	Medical Monitoring at the Iowa Army Ammunition Plant (conducted by the University of Iowa)
Amchitka Island:	Amchitka Workers Medical Surveillance Program (conducted by the State of Alaska Department of Environmental Conservation and the Alaska State District Council of Laborers)
ID (includes	Medical Surveillance for Former INEEL Workers (conducted by Paper,

ANL-W):	Allied-Industrial, Chemical, and Energy International Union)
NV:	Medical Surveillance for Former Department of Energy Workers at the Nevada Test Site (conducted by Boston University)
OR:	Medical Surveillance Program for Construction Workers at Oak Ridge (conducted by the University of Cincinnati)
	Medical Surveillance of Current and Former Workers and the Department of Energy's Gaseous Diffusion Plants (conducted by Paper, Allied-Industrial, Chemical and Energy International Union)
RF:	Rocky Flats Former Worker Screening Program (conducted by University of Colorado Health Sciences Center)
RL:	Hanford Building Trades Medical Screening Program (conducted by the Center to Protect Workers' Rights)
	Former Hanford Worker Medical Monitoring Program (conducted by the University of Washington)
SR:	Augusta Building Trades Medical Screening Program (conducted by Center to Protect Workers' Rights)
	Savannah River Site Former Production Worker Health Project (conducted by the Medical University of South Carolina)

Attachment B

HUMAN SUBJECTS PROJECT COMPLIANCE REVIEW
CHECK LIST

CBeIRB No. **Date of Review:**

Project Title:

Principal Investigator:

Others in Attendance:

Chapter 12 Review Team - Names and CBeIRB Association

Conditions of Review:

Location

Set-Up

Subject Population:

Number of Subjects:
General Age Range:
Equitable Selection:
Is the choice of subjects appropriate for goals of the study?
Inclusion/Exclusion criteria met?
Is the inclusion of a vulnerable population justified and conducted in compliance with 10 CFR 745? (DOE considers workers/employees to be vulnerable populations.)
Do any conditions exist that might pose special medical, ethical or legal problems?

Subject Recruitment:

Is the process used to recruit subjects appropriate for the study, free of coercion and undue influence?
Are the solicitations/advertisements used to recruit subjects accurate and clearly written in layman terms?

Procedures:

Is the current approved protocol available at the study site and read by the study team?
Are procedures compliant with federal regulations and consistent with the approved protocol?

PROCESS OF CONSENT:

Is the currently approved consent form being used?

A. **Capacity to Consent: Do subjects have the capacity to consent?**

In research involving more than minimal risk, capacity to consent should be determined by a psychiatrist, clinical psychologist, or other qualified professional not otherwise involved in the research. Individuals who lack the capacity to consent may participate in research only if consent is given on their behalf by a legally authorized representative.

B. Personnel Inviting Participants: How, and by whom, is informed consent obtained?

Individuals authorized to solicit consent shall sign the consent form confirming that the prospective subject was provided the necessary information and that any questions were answered.

C. Process of Consent: How and where is the consent process taking place? Is it structured to enhance independent and thoughtful decision-making? Are steps taken to avoid coercion or undue influence?

Consider: a) the environment and location where informed consent is solicited; b) the timing of the process (e.g., in relation to hospital admission, work situation, stressful events); c) involvement of someone other than the investigators to help explain the research; and d) opportunity (ample time) for the prospective subjects/representatives to discuss participation in the research with family, friends, or their advisors before signing the consent form.

D. Comprehension of the Information Provided: How, and by whom, is it determined that the subjects or their legally authorized representatives understand the information provided?

The investigator should have an adequate plan in place to ensure existence of an acceptable level of comprehension before consent is documented. Willingness to sign the consent form is not an adequate demonstration of a subject's understanding. Some investigators try to determine the level of comprehension by questioning subjects about the research. This approach is useful with children and adolescents, as well as with adults of uncertain capacity to consent.

E. Translation: Is translation of the consent form required? Are subjects able to comprehend the information provided without translation? How, and by whom, is it determined whether the subjects or their legally authorized representatives understand the information provided?

F. Information Withheld from Subjects: Is any information about the research withheld from the subjects? If so, explain and justify the nondisclosure and describe plans for post-study debriefing.

Any nondisclosure, which should have been approved by the CBeIRB, may not exclude information that a reasonable person would want to know in deciding whether to participate in the research. The alteration must be approved to ensure: 1) the research involves no more than minimal risk to the subjects; 2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; 3) the research could not practicably be carried out without the waiver or alteration; and 4) when appropriate, the subjects will be provided with pertinent information after participation.

G. Does the informed consent procedure incorporate the following basic elements? (Check all that apply.)

____ A simple and clear explanation of the purpose of the research and chronological description of the procedures the subject will be involved in, including an identification of those that are experimental.

____ A simple and clear statement that subject's participation is voluntary.

____ A description of the attendant discomforts and risks.

____ A description of possible benefits.

____ An explanation of compensation or cost to the subjects.

____ A statement describing how privacy of data or personal information will be maintained.

____ A disclosure of appropriate alternative procedures that might be advantageous for the subject.

____ An offer to answer any inquiries concerning the procedures.

____ An instruction that the subject is free to withdraw his or her consent and to discontinue participation on the project or activity at any time.

____ Available sources of information and an explanation that the subject is free to ask questions at any time during the study.

____ Adequate documentation of informed consent.

____ Documentation of the method for informing subjects of the results of their participation in the research.

H. Will subjects be given a copy of the signed consent form? (If not, please explain)

Records Management:

Are records prepared according to funding agency requirements, Good Clinical Practice Guidelines, and institutional requirements?

Is completion of human subjects training documented for all project staff?

Have project procedures been read by staff and documented to the files?

Is there a manual of Operations?

Are required documents completed correctly?

Are required documents consistent with other related information?

Is a Medical Monitoring Plan in place for Phase 1 and 2 small-scale early clinical trials?

Are consent forms signed and dated with all signatories names printed/typed?

Are all adverse events properly reported and resolved?

Are data management plans consistent with requirements of the study adhered to by all project staff?

Have all modifications/addenda been approved by the CBeIRB prior to implementation?

Have adverse events been reported promptly to the CBeIRB?

Are subject accruals properly reported to the CBeIRB?

General Overall Impression:

Do the PI and the project staff have the training and experience to conduct the study? Does the PI appear to be in control of the study?

Is the study design, as approved by the CBeIRB, being strictly adhered to?

Is the consent process clear to subjects and without problems?

Is the confidentiality, privacy, and identity of the subjects adequately protected?

Have changes been made to the protocol that are not approved by the CBeIRB?

Does the PI appear to freely and clearly communicate with the subjects?

Are expectations of participation and procedures clear to the subjects and project staff?

Do subjects appear to be comfortable with the requirements of participation and free to seek clarification at every point in the process? Do they understand they may quit the study at any time?

Are children allowed to assent for themselves? How are children treated by the PI and other project staff? By their parents or guardian?

Conclusions:

Is there any item or situation that requires immediate attention?

Does the item or situation impact the welfare or well being of the subjects?

Does the situation call for stop work on the project? Notification to others?

Recommendations for Changes or Improvement:

Schedule for Resolution:
Immediate Action

Short Term

Long Term

Final Comments:

Attachment C

Exempt Research Activities

From 10 CFR 745.101(b)

Unless otherwise required by federal department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from IRB review:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

(ii) 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.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, 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.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) Public benefit or service programs;

(ii) Procedures for obtaining benefits or services under those programs;

(iii) Possible changes in or alternatives to those programs or procedures; or

(iv) Possible changes in methods or levels of payment for benefits or services under those programs.

Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Attachment D

Expedited Review Categories

From Federal Register 11/9/98

Research activities that present no more than minimal risk to human subjects and involve only procedures listed in one or more of the following categories may be reviewed by the IRB through the expedited review procedure. The categories in this list apply regardless of the age of subjects, except as noted.

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) from other adults and children,² considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) Hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, □oppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects 45 CFR 46.101 (b)(2) and (b)(3). This listing refers only to research that is not exempt.)

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

(b) Where no subjects have been enrolled and no additional risks have been identified; or

(c) Where the remaining research activities are limited to data analysis.

(9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Expedited review may not be used

- Where identification of subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

- For classified research involving human subjects.

Attachment E

Elements of Informed Consent

Basic Elements of Informed Consent

The researcher shall provide ***all*** of the following information to each subject when seeking informed consent:

a. 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.

b. A description of any reasonably foreseeable risks or discomforts to the subject.

c. A description of any benefits to the subject or to others that may reasonably be expected from the research.

d. Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

e. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

f. For research involving more than minimal risk, an explanation as to whether any compensation and/or medical treatment is available if injury occurs and, if so, what they consist of, or where further information may be obtained.

g. An explanation of whom to contact for answers to pertinent questions about the research, about the research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

h. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that 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

When appropriate, one or more of the following elements of information shall also be provided to each subject:

a. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable.

b. Anticipated circumstances under which the subject's participation may be terminated by the investigator without obtaining the subject's consent.

c. Any additional costs to the subject that may result from participation in the research.

d. The consequences of a subject's decision to withdraw from the research, and procedures for orderly termination of participation by the subject.

e. 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.

f. The approximate number of subjects involved in the study.

g. Any additional information that would meaningfully add to the protection of the rights and welfare of subjects.

Note: These required elements of informed consent are not intended to preempt any applicable federal, state or local laws that require additional information to be disclosed for informed consent to be legally effective.

Attachment F

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment, or who is requested to consent on behalf of another, has the right to:

1. Be informed of the nature and purpose of the experiment.

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.

3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment, if applicable.

4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.

5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.

6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment, if complications should arise.

7. Be given the opportunity to ask any questions concerning the experiment or the procedures involved.

8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

9. Be given a copy of the signed and dated written consent form.

10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

11. Be informed that, unless confidentiality is specifically waived by a participant, the identity of a study participant will be kept confidential; the name and other identifying information will not be released to anyone beyond those directly responsible for conducting the research.

If at any time you have any questions regarding a research study, the researcher or his/her assistant will be glad to answer them. You may also seek assistance from the Central Beryllium Institutional Review Board (CBeIRB), which was established for the protection of volunteers in research projects. The Chair of the CBeIRB or the CBeIRB Administrator, may be reached by calling (865) 576-1725 from 8:00 a.m. until 4:30 p.m., Monday through Friday, or writing to the CBeIRB Oak Ridge Associated Universities, P.O. Box 117, MS 44, Oak Ridge, TN 37831-0117.

ATTACHMENT G

FORMS

APPPLICATION FOR CONTINUING REVIEW/PROGRESS REPORT

For Approval to Involve

HUMAN SUBJECTS IN RESEARCH

Expedited or Full Board Review for Continuing Approval

Central Beryllium Institutional Review Board

Contact
Becky Hawkins, CBeIRB Administrator
Tel: (865) 576-1725
Fax: (865) 576-9557
E-mail: hawkinsb@orau.gov

Continuing Review - Application To Involve Human Subjects In Research

Federal policy requires that all research involving human subjects be reviewed by the Central Beryllium Institutional Review Board (CBeIRB) *within 12 months or less of the previous approval*. Continuing review must be substantive and meaningful to protect the rights and welfare of research subjects.

The CBeIRB must review ongoing Be-related research with respect to potential benefits, risks, adequacy of consent forms and other criteria for safeguarding human subjects. Comprehensive review is mandatory at the time of continuing review as well as the initial application. New subjects may not be enrolled and research activities may be suspended if a continuing review approval is not issued before the expiration date of the most current approval.

Checklist

Required Documentation for Continuing Review Application

____ **Continuing Review Application** (signed by PI)

____ **Current Statement of Work, if applicable**

____ **Revisions, amendments, appendices to previously approved protocol**

____ **All Informed Consent Forms currently approved for use**

____ **Documentation of PI or project's primary staffs' human subjects training**

____ **Publications within current reporting period**

____ **Any other information that will support the review**

____ **A list of documents submitted, individually identified** (i.e, recruitment letters, advertisements, publications, questionnaires, informed consent forms, etc.)

If Applicable, provide current:

____ **IRB Review from other involved Institutions, documentation of approval**

____ **Advertisement, flyers, brochures, or other solicitation for volunteers**

____ **Questionnaires/surveys**.

____ **Other documents associated with the program**

APPLICATION FOR CONTINUING REVIEW

CBe IRB No.	**FWA #00005031**
Project/TaskTitle:	
Names, project ID numbers, and Expiration date(s) of approvals from other IRB's reviewing this document:	

Principal Investigator: **Co-Principal Investigator or Alternate Contact**

Name:	**Name:**
Phone/Fax/e-mail:	**Phone/Fax/e-mail:**
Address:	**Address**

Investigator Assurance

I certify that the information provided in this application is complete and correct. As Principal Investigator, I acknowledge that I am responsible for the ethical conduct and performance of this project, for protecting the rights and welfare of human subjects, and for strict adherence to any stipulations imposed by the CBe Institutional Review Board in accordance with applicable Federal, State, and Institutional policies and procedures. I will:

- **Conduct this project using only qualified personnel in accordance with the approved protocol.**
- **Obtain CBeIRB approval before implementing any changes to the approved protocol, consent form, or supporting documents (except in an emergency, if necessary, to safeguard the immediate well being of human subjects.**
- **Secure legally effective Informed Consent from subjects or their responsible representative, using only the currently approved consent form.**
- **Immediately report significant or untoward adverse effects to the CBeIRB.**
- **Provide documentation of human subjects training for key project staff**
- **Report any potential conflict of interest for investigator staff or collaborating institutions.**

_____ _____ _____

Principal Investigator (Printed) Signature Date Submitted

This Section to be completed by the CBe Institutional Review Board

Review conducted under: Full Board _____ Expedited _____ Exempt_____ procedures in accordance with
Federal Regulation 45 CFR 46, DOE 10 CFR 745, and 10 CFR 850
<u>Approved for Continuation</u>: Yes _____ No_____ Resubmit Application. This project may not continue without CBeIRB approval
Conditions of Approval:

Approval Valid through_____, unless otherwise revised before that date.
_____ _____ _____ **Name (printed and signed)** **Title** **Date**

Project Start Date: _____ Anticipated End Date: _____

Current Funding Period Reported: _____ through _____
Estimated Future Funding for Human Subjects Involvement: $_____

Estimated Funding for Human Subjects Involvement for the next funding period: $_____

A. Research Project Current Status:

1. What is the present status of your research project?

____ Awaiting funding. Anticipated start date: _____.
____ Anticipate enrolling new subjects and/or approaching prospective subjects during this approval period.
____ No human subject involvement expected during this approval period.
____ Human subject contact will begin during the next approval period.
____ Follow up on previously enrolled subjects.
____ Follow up on previously enrolled subjects and no new subjects will be involved.
____ Analyzing data only - no further human subjects involvement.
____ Project completed? Submit Final Report. Your study will be closed in the CBeIRB files.
____ Other:

2. Are you requesting, or planning, any modifications to the previously approved protocol, consent form, or other supporting documents? Yes_____ No _____

   a. Explain the modifications and provide an updated protocol and supporting documents.
   b. Explain the effects of the requested modifications on risks, benefits to subjects, including any changes to the consent procedures.

3. If the research project has been initiated, please submit a Project Progress Report (if applicable) and reply to the following questions:

   a. Number of human subjects enrolled in the project to date (total)
   b. Number of human research subjects enrolled this report period _____
   c. Number of new human research subjects enrolled next report period _____ (planned)
   d. Has there been any difficulty obtaining/retaining subjects or obtaining informed consent during the previous approval period? Yes__ No __ *If yes, please describe.*

____ Approximately how many potential subjects have refused participation?
____ How many subjects have withdrawn participation at their own request?
____ How many subjects have withdrawn participation at the project's request?

a. Were there any adverse effects, unanticipated risks, or complaints related to the involvement of research subjects? ___Yes ___No. *If yes, was an Adverse Event Report filed? Describe the circumstances and corrective actions taken.*

4. Is there any new information since previous report that might affect the risk/benefit ratio for new subjects or subjects already participating in the research, or their willingness to participate in the research (e.g., information or adverse effects resulting from other research)?Yes ____ No ____ *If yes, please describe.*

5. Have there been any significant new findings (positive or negative) that should be disclosed to subjects who have participated in the study?
Yes ____ No ____ *If yes, please describe.*

6. Has any change been made since the previous review that might constitute a conflict of interest, such as a change in collaborating institutions or principal investigators that might have a financial interest in the outcome of this research?

B. Informed Consent

Please review your most recently approved informed consent forms currently in use for this project.

Based on your experience in the conduct of this study, are the actual risks and benefits still adequately addressed at all stages in the informed consent process?

The consent form must include the basic elements of informed consent as outlined in 45 CFR 46 and 10 CFR 745.

C. Involvement of Other Institutions

If applicable, documentation of current IRB approval must be provided for collaborating institutions.

D. Health Insurance and Portability Accounting Act (HIPAA)

If applicable, confirm that institutions involved in this research are in compliance with the requirements of the DHHS Health Insurance Portability and Accountability Act (45 CFR Parts 160 and 164).

E. Future Activities

Summarize the scope of activities planned for the next review period that involve human subjects. If other institutions are involved, describe activities that will take place at those institutions, as well.

Human Subjects Training: Documentation of human subjects training for all key project staff must be completed before this application will be accepted for review.

Documentation of human subjects training for all key project staff is:

Attached to this application:_____

Current and on File in the CBeIRB Office: _____

Administrative Requirements:

- All contact documents (consent forms, letters, etc.) must be paginated in a footer in the style of "1 of n," where "n" is the total number of pages in the document. Dates should be included in this footer adequately identify each document and include its most recent revision date.
- Names of **ALL** signatories on the Application, consents, etc., must be printed or typed.
- **ALL** signatures must be dated.
- All contact documents (consents, letters, informational materials) must be in size 10 font or greater.
- Double-sided printing is recommended for all final versions of contact documents, consents, and letters.

APPPLICATION FOR CONTINUING REVIEW/PROGRESS REPORT

For Approval to Involve

HUMAN SUBJECTS IN RESEARCH

Expedited or Full Board Review for Continuing Approval

Central Beryllium Institutional Review Board

Contact
Becky Hawkins, CBeIRB Administrator
Tel: (865) 576-1725
Fax: (865) 576-9557
E-mail: hawkinsb@orau.gov

Continuing Review - Application To Involve Human Subjects In Research

Federal policy requires that all research involving human subjects be reviewed by the Central Beryllium Institutional Review Board (CBeIRB) *within 12 months or less of the previous approval*. Continuing review must be substantive and meaningful to protect the rights and welfare of research subjects.

The CBeIRB must review ongoing Be-related research with respect to potential benefits, risks, adequacy of consent forms and other criteria for safeguarding human subjects. Comprehensive review is mandatory at the time of continuing review as well as the initial application. New subjects may not be enrolled and research activities may be suspended if a continuing review approval is not issued before the expiration date of the most current approval.

Checklist

Required Documentation for Continuing Review Application

____ **Continuing Review Application** (signed by PI)

____ **Current Statement of Work, if applicable**

____ **Revisions, amendments, appendices to previously approved protocol**

____ **All Informed Consent Forms currently approved for use**

____ **Documentation of PI or project's primary staffs' human subjects training**

____ **Publications within current reporting period**

____ **Any other information that will support the review**

____ **A list of documents submitted, individually identified** (i.e, recruitment letters, advertisements, publications, questionnaires, informed consent forms, etc.)

If Applicable, provide current:

____ **IRB Review from other involved Institutions, documentation of approval**

____ **Advertisement, flyers, brochures, or other solicitation for volunteers**

____ **Questionnaires/surveys**.

____ **Other documents associated with the program**

APPLICATION FOR CONTINUING REVIEW

CBe IRB No.	FWA #00005031
Project/TaskTitle:	
Names, project ID numbers, and Expiration date(s) of approvals from other IRB's reviewing this document:	

Principal Investigator: **Co-Principal Investigator or Alternate Contact**

Name:	Name:
Phone/Fax/e-mail:	Phone/Fax/e-mail:
Address:	Address

Investigator Assurance

I certify that the information provided in this application is complete and correct. As Principal Investigator, I acknowledge that I am responsible for the ethical conduct and performance of this project, for protecting the rights and welfare of human subjects, and for strict adherence to any stipulations imposed by the CBe Institutional Review Board in accordance with applicable Federal, State, and Institutional policies and procedures. I will:

- **Conduct this project using only qualified personnel in accordance with the approved protocol.**
- **Obtain CBeIRB approval before implementing any changes to the approved protocol, consent form, or supporting documents (except in an emergency, if necessary, to safeguard the immediate well being of human subjects.**
- **Secure legally effective Informed Consent from subjects or their responsible representative, using only the currently approved consent form.**
- **Immediately report significant or untoward adverse effects to the CBeIRB.**
- **Provide documentation of human subjects training for key project staff**
- **Report any potential conflict of interest for investigator staff or collaborating institutions.**

_____ _____ _____

Principal Investigator (Printed) Signature Date Submitted

This Section to be completed by the CBe Institutional Review Board

Review conducted under: Full Board _____ Expedited _____ Exempt_____ procedures in accordance with
Federal Regulation 45 CFR 46, DOE 10 CFR 745, and 10 CFR 850
Approved for Continuation: Yes _____ No_____ Resubmit Application. This project may not continue without CBeIRB approval
Conditions of Approval:

Approval Valid through_____, unless otherwise revised before that date.
_____ _____ _____ **Name (printed and signed)** **Title** **Date**

Project Start Date: _____ Anticipated End Date: _____

Current Funding Period Reported: _____ through _____
Estimated Future Funding for Human Subjects Involvement: $_____

Estimated Funding for Human Subjects Involvement for the next funding period: $_____

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____ Awaiting funding. Anticipated start date: _____.
____ Anticipate enrolling new subjects and/or approaching prospective subjects during this approval period.
____ No human subject involvement expected during this approval period.
____ Human subject contact will begin during the next approval period.
____ Follow up on previously enrolled subjects.
____ Follow up on previously enrolled subjects and no new subjects will be involved.
____ Analyzing data only - no further human subjects involvement.
____ Project completed? Submit Final Report. Your study will be closed in the CBeIRB files.
____ Other:

2. Are you requesting, or planning, any modifications to the previously approved protocol, consent form, or other supporting documents? Yes_____ No _____

   a. Explain the modifications and provide an updated protocol and supporting documents.
   b. Explain the effects of the requested modifications on risks, benefits to subjects, including any changes to the consent procedures.

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   c. Number of new human research subjects enrolled next report period _____ (planned)
   d. Has there been any difficulty obtaining/retaining subjects or obtaining informed consent during the previous approval period? Yes__ No __ *If yes, please describe.*

____ Approximately how many potential subjects have refused participation?
____ How many subjects have withdrawn participation at their own request?
____ How many subjects have withdrawn participation at the project's request?

a. Were there any adverse effects, unanticipated risks, or complaints related to the involvement of research subjects? ___Yes ___No. *If yes, was an Adverse Event Report filed? Describe the circumstances and corrective actions taken.*

4. Is there any new information since previous report that might affect the risk/benefit ratio for new subjects or subjects already participating in the research, or their willingness to participate in the research (e.g., information or adverse effects resulting from other research)?Yes ____ No ____ *If yes, please describe.*

5. Have there been any significant new findings (positive or negative) that should be disclosed to subjects who have participated in the study?
Yes ____ No ____ *If yes, please describe.*

6. Has any change been made since the previous review that might constitute a conflict of interest, such as a change in collaborating institutions or principal investigators that might have a financial interest in the outcome of this research?

B. Informed Consent

Please review your most recently approved informed consent forms currently in use for this project.

Based on your experience in the conduct of this study, are the actual risks and benefits still adequately addressed at all stages in the informed consent process?

The consent form must include the basic elements of informed consent as outlined in 45 CFR 46 and 10 CFR 745.

C. Involvement of Other Institutions

If applicable, documentation of current IRB approval must be provided for collaborating institutions.

D. Health Insurance and Portability Accounting Act (HIPAA)

If applicable, confirm that institutions involved in this research are in compliance with the requirements of the DHHS Health Insurance Portability and Accountability Act (45 CFR Parts 160 and 164).

E. Future Activities

Summarize the scope of activities planned for the next review period that involve human subjects. If other institutions are involved, describe activities that will take place at those institutions, as well.

Human Subjects Training: Documentation of human subjects training for all key project staff must be completed before this application will be accepted for review.

Documentation of human subjects training for all key project staff is:

Attached to this application:_____

Current and on File in the CBeIRB Office: _____

Administrative Requirements:

- All contact documents (consent forms, letters, etc.) must be paginated in a footer in the style of "1 of n," where "n" is the total number of pages in the document. Dates should be included in this footer adequately identify each document and include its most recent revision date.
- Names of **ALL** signatories on the Application, consents, etc., must be printed or typed.
- **ALL** signatures must be dated.
- All contact documents (consents, letters, informational materials) must be in size 10 font or greater.
- Double-sided printing is recommended for all final versions of contact documents, consents, and letters.

(Sample) Cooperative IRB Review Agreement
(for projects subject to review by multiple IRBs)

Name of Institution Providing IRB Review - IRB of Record (Institution A):

Central Beryllium Institutional Review Board
Oak Ridge Associated Universities
P.O. Box 117
Oak Ridge, Tennessee 37831-0117
Federal Wide Assurance (FWA): 1394

Name of Institution Relying on Designated IRB of Record (Institution B):

The Officials signing below agree that Institution B will rely on Institution A for continuing review and oversight of the following human subject research protocols:

Title:
IRB Number:
Principle Investigator:
PI Institution:

Institution A will provide continuing review and oversight for the projects cited above in accordance with the attached policies and procedures and the requirements and obligations of the Federal Wide Assurances held by both Institutions. Institution A acknowledges the right and responsibility of Institution B to provide preliminary review and comment as a necessary element of this process while both IRBs recognize the final authority of Institution A as IRB of Record. Institution A will report its findings and actions to Institution B and will provide sections of the minutes of its meetings that relate to the project(s) identified to Institution B upon request. Institution B will fully support and comply with Institution A's determinations in accordance with the requirements and obligations of this agreement. In the case of unresolved disputes, a final determination will be made by the U. S. Department of Energy Office of Science Program Manager for Protection of Human Subjects in Research. This document will be kept on file at both institutions and provided to DOE/Office of Science.

Institution A

_____ Date: _____
Signatory Official/Title (printed/typed and signed)

Institution B

_____ Date: _____
Signatory Official/Title (printed/typed and signed)

Cooperative Research Agreement Policies and Procedures

Central Beryllium Institutional Review Board
and

The following guidelines, policies and procedures are provided for the Principal Investigators (PI) and Institutional Review Boards (IRB) involved in the Cooperative Agreement between the Central Beryllium IRB (CBeIRB) and the _____for review of the Former Worker Medical Monitoring Programs funded by the Department of Energy and conducted at_____. The PI is responsible for complying with the policies and procedures required by their Institutional IRB.

Specific instructions, notification requirements, forms, and procedures are provided for routine activities that require IRB approval such as amendments or modifications to the protocol or consent, serious adverse events, continuing and compliance reviews, and project closure.

As IRB of Record, the CBeIRB is the first point of contact for the PI. Items not addressed within this document should be discussed with the CBeIRB, which will provide initial assessment and guidance. The CBeIRB will consult with and/or provide notification to the Site IRB at its discretion.

Amendments, Modifications to the Protocol, Consent or Supporting Documents, Significant New Findings and Minor Adverse Events

All amendments, modifications or changes to the protocol, consent or supporting documents and significant new findings and minor adverse events must be reviewed and approved by the CBeIRB. Significant new findings may be described as "*any new finding, good or bad that might affect a subject's willingness to continue their participation in a study or significantly change the approved study protocol*." Minor adverse events are generally described in the consent as *"those anticipated or no more severe than expected, such as a mild fainting spell following a blood draw or, data management errors or problems where subject identification is not seriously compromised."* (Procedures for reporting serious adverse events are provided below). Standard procedures for submitting a request for review are:

PI	• Contacts CBeIRB and submits request for review ▪ CBeIRB (Original package including Application form and required backup) ▪ Site IRB (Information Copy) ▪ Institutional IRB (Information Copy)
Site IRB	• Provides comments/recommendations to CBeIRB and PI within 5 working days
CBeIRB	• Determines if IRB review is required and level of review. • Corresponds with PI and other IRBs, if necessary, to resolve issues. • Makes final determination: ▪ If approved, provides notice of approval to PI and Site IRB ▪ If disapproved or conditionally approved, provides PI and Site IRB with written rational for denial, or describes requirements, conditions and timeline for final approval.
PI	• If approved: ▪ Submits CBeIRB-approved packaged to Institutional IRB. • If disapproved or conditionally approved: ▪ May appeal disapproval and repeat the process. ▪ Meets the conditions for approval and re-submits to CBeIRB

CBeIRB	• Makes final determination and provides documentation to PI and Site IRB

Serious Adverse Events

A serious adverse event (AE) is described as "*an event or unanticipated problem involving serious bodily, psychological, social, or emotional harm to subjects or others, or serious or continuing noncompliance with 45 CFR 46 or the requirements of IRB approval"*. In most instances, the PI will notify the CBeIRB to determine the appropriate action. However, the immediacy and seriousness of an event, or availability of the CBeIRB, could alter the sequence in which the following procedures take place. For instance, an event that posed immediate serious threat or harm to subjects might require that the Site IRB convene immediately to assist the PI in determining the appropriate action. The Site IRB would inform the CBeIRB of their findings and recommendations as soon as possible. The CBeIRB would then issue their official finding and required action for the PI and complete the prescribed process. The PI is responsible for complying with their institutional requirements for reporting serious adverse events. The procedures for handling serious adverse events under this agreement are:

PI	• **Immediately Notifies:** ▪ CBeIRB. ▪ Site IRB (Information Copy). ▪ Institutional IRB (Provides information copy and complies with Institutional requirements for reporting serious adverse events).
CBeIRB	• Makes initial assessment to determine seriousness of event and risk to subjects • If stop work order is issued, immediately notifies PI, Site IRB, Sponsor, and Dr. Susan Rose • If a stop work order is not required, provides guidance to PI
PI	• Reviews AE procedures and submits formal adverse event report ▪ CBeIRB (Original). ▪ Site IRB (Information Copy). ▪ Institutional IRB (Provides information copy and complies with Institutional requirements for reporting serious adverse events).
Site IRB	• Provides comments/concerns to CBeIRB within 1-5 working days, as determined by the CBeIRB.
CBeIRB	• Corresponds with PI and Site IRB to resolve any remaining issues • Makes final determination regarding approval to continue or not • Provides PI and site IRB with documentation of Approval to Proceed
PI	• Submits CBeIRB-approved packaged to Institutional IRB, if required.

Continuing Review

Continuing review must be conducted within 12 months or less of the original approval date as determined by the IRB of Record at its initial review. Continuing review must be substantive and thorough and must be completed before the annual expiration date in order for the project to remain in compliance with the terms of approval. At a minimum, the PI must submit a continuing review form, current statement of work, all consent forms currently in use on the project and, if available, the most current project progress report. The PI should provide any information that will assist the CBeIRB in its review of the current protocol.

CBeIRB	• Notifies PI of requirements for continuation at least 8 weeks in advance of the current expiration date, particularly if the project requires full board review.
PI	• Submits request for Continuing Review at least 4 weeks before the expiration date. ▪ CBeIRB (Original) ▪ Site IRB (Information Copy) ▪ Institutional IRB (Information Copy)
Site IRB	• Provides concerns/recommendations to CBeIRB and PI within 5 working days
CBeIRB	• Identifies revisions or other issues that require resolution before approval may be granted. • Makes final determination to approve or disapprove. If approved, notifies PI and Site IRB. • If disapproved or approved conditionally, provides rational, conditions and timeline for final approval to the PI and Site IRB.
PI	• If approved: ▪ Submits CBeIRB-approved packaged to Institutional IRB. • If disapproved or conditionally approved: ▪ May appeal disapproval and repeat the process. ▪ Meets the conditions for approval and submits to CBeIRB
CBeIRB	• Makes final determination and provides documentation to PI and Site IRB

Compliance Review

The CBeIRB may conduct compliance reviews of these projects as it deems necessary, using the Compliance Review Check List and Report Form. Results of compliance reviews should be reported to the PI and Site IRB in a timely manner to promote early resolution of any outstanding issues that might arise from the review.

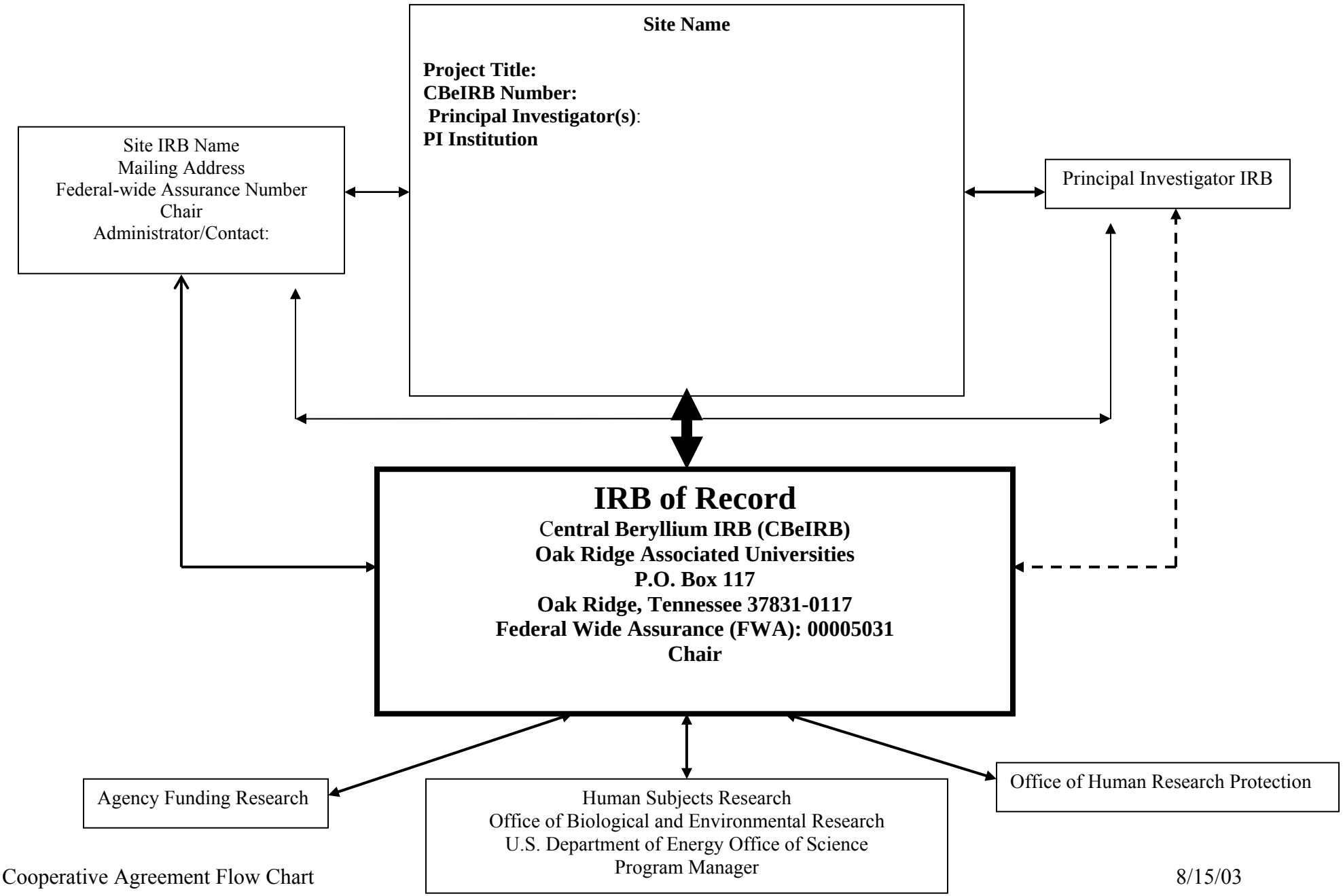
Final Report and Project Closure

A final report is required for all projects at the time of project completion. A project progress or final report and any other pertinent documentation should be submitted with Form HS-5. PI's should ensure at the time of project closeout that they have fully met the terms and conditions of the approved protocol, in particular the disposition of human biological materials or data that are associated with personal identifiers.

PI	• Submits request for review ▪ CBeIRB (Original) ▪ Site IRB (Information Copy) ▪ Institutional IRB (Information Copy)
Site IRB	• Provides comments/recommendations to CBeIRB and PI within 5 working days

CBeIRB	• Notifies PI if it is determined that further information is required • Corresponds with PI and other IRBs, as needed, to resolve final concerns • Accepts final report and closes file • Notifies PI, Site IRB, and DOE/SC
PI	• Submits notification of project completion to the Institutional IRB.

Cooperative IRB Review - Flow Chart (Option X)



Modification, Change, New Finding or Minor Adverse Event (draft form 7/20/03)

CBeIRB Authorized Signature: _____ **Date approved**: _____**Denied:**_____ **Comments**:

The original Continuing Review date remains in effect for this protocol.

Finding

Reviewed in accordance with 45 CFR 46, DOE 10 CFR 745, and 10 CFR 850

Protocol ☐

Consent ☐

New ☐

Other ☐

Read this form carefully and address all items apply to the modification(s) or new finding(s). Modifications may not be implemented until approved by the CBeIRB. Please call the CBeIRB Administrator at (865) 576-1725 for assistance. Provide a signed copy of this form and supporting documents as noted below.

Date: _____ **CBeIRB No.:** _____

Project Title: _____

Principal Investigator: _____

Dept: _____ Phone: _____ Fax: _____ Email: _____

Contact person: _____ Phone: _____ Fax: _____ Email: _____

Describe any change or increase in risk to subjects that might result from the modification or finding and explain how risks will be minimized. Address all items below that might be affected by this change (i.e., a change in procedure often requires revisions to the consent and other information provided to subjects).

☐ **No change in risk to subjects.**
☐ **Change to consent is not required. Explain below under appropriate topic.**
☐ **Additional or different risk to subjects. Explain below under appropriate topic.**

☐ **AMENDMENT TO THE PROTOCOL:** Describe modifications, omissions, or additions to the current approved protocol. Attach amendment, current statement of work and supporting documents.

☐ **CHANGE IN STUDY PURPOSE AND SCOPE:** Describe the change in study purpose/scope and explain why the change is necessary.

☐ **CHANGE IN RESEARCH PROCEDURES INVOLVING SUBJECTS:** Describe the change in research procedures involving subjects and provide an explanation.

☐ **CHANGE OR ADDITION TO PROJECT DOCUMENT, such as advertisements, questionnaires, and data management plans, etc.:** Explain why changes are required. Highlight the original copy and submit with the new version. If new, explain the purpose for the document; describe how it will be used and by whom.

Oak Ridge Associated Universities P.O. Box 117, MS-44 Oak Ridge, TN 37831-0117
(P): 865-576-1725 (F: 865-576-9557 e-mail: hawkinsb@orau.gov

Modification, Change, New Finding or Minor Adverse Event (draft form 7/20/03)

☐ **NEW OR SIGNIFICANT FINDING:** Describe the new or significant finding, how it will increase or change the risk to subjects and possibly impact their willingness to participate.

☐ **CHANGE IN BIOLOGICAL MATERIALS/SAMPLES OR SUPPLIER:** Describe the change in type, identification, or source of biological materials, samples, or tissues derived from humans. Explain the reason for the change and describe additional requirements for subject protections that may be required.

☐ **CHANGE IN SUBJECT POPULATION and/or METHOD OF RECRUITMENT:** Explain the proposed change in subject population and/or the method of recruitment. If different from the approved protocol, include inclusion and exclusion criteria, number and age, gender, vulnerability, approach and method of recruitment.

☐ **REVISION TO CONSENT PROCESS, FORM OR ORAL SCRIPT:** Provide an explanation for the revision. For revised documents, highlight changes on one copy and submit with revised copy. If new, please state.

☐ **CHANGE IN INVOLVED INSTITUTIONS OR SITES:** Explain the change in institution or site involvement. Submit a current IRB approval or letter of cooperation for each institution or site. Provide IRB contact information as coordination between institutions may be required to complete this review.

☐ **ADVERSE EVENTS:** Use this form to report changes instituted as a result of "minor" adverse events only (those noted in the consent as anticipated or no more severe than would normally be expected, such as minor bruising or fainting from a blood draw). Briefly describe the event and the changes being implemented in response to the event. Evaluate the need for revised consent. "Minor" adverse events must be reported during annual continuing review or upon study completion, whichever occurs first.

Note: Serious events (unexpected or more severe than anticipated) must be reported <u>immediately</u> to the CBeIRB using the CBeIRB "Adverse Event Report Form." Consult with the CBeIRB Administrator to determine seriousness of the event.

☐ **CONFLICT OF INTEREST:** Describe any changes in the financial or professional interest of members of the research team or other institutions collaborating in this study that might constitute a conflict of interest. Consult with CBeIRB if in doubt.

☐ **CHANGE IN PRINCIPAL INVESTIGATOR:** Provide new PIs current CV/resumé and documentation of Human Subjects training.

☐ **CHANGE OF CO-INVESTIGATORS.** Provide list (full name/degree/ affiliation) of new investigators and of investigators no longer associated with the study/project..

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☐ **OTHER CHANGES:** Describe the change, discuss possible impact to subjects and provide supporting documentation.

Current PI Name:_____ _____ **Phone:**_____

Fax:

Printed **Email:** _____

Effective Start Date of Current PI on this Project:_____

I understand that as Principal Investigator, I am responsible for the conduct and ethical performance of this project, for protecting the rights and welfare of human subjects, and for strict adherence to any stipulations imposed by the CBeIRB in accordance with applicable Federal, State, and Institutional policies and procedures. I will:

X Conduct this project using only qualified personnel in accordance with the approved protocol.
X Obtain CbeIRB approval before implementing any changes to the approved protocol, consent, or supporting documents (except in an emergency to safeguard the immediate well being of subjects).
X Secure legally effective Informed Consent from subjects or their responsible representatives, using only the currently approved consent form.
X Immediately report serious or untoward adverse effects to my institution's and/or the CBeIRB as applicable.
X Provide documentation of human subjects training for key project staff.
X Report any potential conflict of interest for my institution's staff or collaborating institutions.

I certify the information provided above is accurate and complete.

Current Principal Investigator Signature :_____
Date:_____

Attachments:

Distribution: Principal Investigator
CBeIRB Members (Expedited/Full Board review)
File

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8/15/03
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SERIOUS ADVERSE EVENT PROCEDURES AND REPORT FORM

HUMAN SUBJECTS RESEARCH

Central Beryllium Institutional Review Board (CBeIRB)

Contact
Becky Hawkins, IRB Administrator
Tel: (865) 576-1725
Fax: (865) 576-9557
E-mail: hawkinsb@orau.gov

Procedure for Handling Serious Adverse Events (SAE)

A Serious Adverse Event (SAE) may be described as "*an unexpected or more serious than anticipated event or problem involving serious bodily, psychological, social, or emotional harm to subjects or others; or serious or continuing noncompliance with human subject regulation 45 CFR 46 or the requirements of IRB approval – including those that occur at collaborating institution..*" Serious events must be reported to the CBeIRB using the following procedures and form.

1. A principal investigator's (PI) first responsibility is to ensure the safety and well being of the subject and/or stabilization of the situation. The PI's initial actions will be determined by the seriousness of the event and imminent danger or risk of further harm to the subject or to others.

2. The PI will **immediately** report the event to the CBeIRB and will provide regular status reports as the event unfolds, particularly in regard to a subject's condition.

3. The CBeIRB Chair and the PI will perform an initial assessment of the event to determine if the situation is serious enough to warrant a stop work order, emergency meeting of the full CBeIRB, involvement of other health or safety committees, or immediate notification to other stakeholders.

4. Within 5 days of the event, the PI will submit a SAE report including the consent form signed by the subject and any revised protocols, consents or supporting documents.

5. The CBeIRB Chair will determine if Full Board review of the event is warranted, but will schedule a meeting with the PI in either case.

6. If the review is conducted under Full Board review and the CBeIRB requires non-substantive revisions or additional information, it may vote to conditionally approve and authorize final approval to the Chair. The Chair will track any remaining requirements to completion.

7. The SAE will be closed out and a final report will be distributed to all stakeholders as required.

CENTRAL BERYLLIUM INSTITUTIONAL REVIEW BOARD

SERIOUS ADVERSE EVENT REPORT

Date of Report:		
Project Title:	**CBeIRB No:**	
Principal Investigator:	**Phone/Fax:**	
Other Investigator(s):	**Phone/Fax:**	
Collaborating Institution(s):		
Collaborating IRB(s):		
Date of Event:	**Location:**	**Time:**

1. DESCRIPTION OF SERIOUS ADVERSE EVENT

The SAE/I was: Moderate _____ Very Severe _____ Fatal_____

No. of subjects involved: Subject's age:

Location where SAE/I took place:

Person attending to subject at the time:

Provide a detailed, chronological description of the SAE. Include the subject's demographic information:

Relationship of the SAE to the protocol: Not related ____ Possibly Related ____Related ____ Unknown____. **Provide a rational for your answer:**

2. Has this kind of event happened before in connection with this study? If yes, explain below.

3. ACTION TAKEN

Provide a detailed description of the immediate and follow-up action taken.

4. TREATMENT PROVIDED TO THE SUBJECT

Date(s) of treatment:

Describe treatment provided to the subject:
Where was care provided?
Describe the subject's recovery and current status:

Who is financially responsible for the treatment?
Sponsor
Subject/Subject's Insurer
Other

5. CHANGES NECESSITATED BY THIS EVENT

Changes in Protocol: Is a change in the protocol necessary to reduce or eliminate further risk?
Yes _____ if yes, attach two copies of the revised protocol with changes in bold on one copy.
No _____ if no, provide a brief rationale for not changing the protocol.

6. CHANGES TO INFORMED CONSENT/ASSENT OR SUPPORTING DOCUMENTS

7. Is the potential for this kind of adverse event described in the currently approved consent form?

Are changes to the consent or other supporting documents necessary in order to better inform and protect the rights and welfare of subjects?

Yes _____If yes, attach two copies of the revised consent or documents with changes in bold on one copy. **Note that no new subjects may be entered until the revised forms are approved.**

No _____ if no, provide a brief rationale.

8. RE-CONSENT/ASSENT

Is it necessary to inform previously consented subjects or their legal representatives of the SAE?

Yes _____ if yes, provide a description and document for notifying subjects.

No _____ if no, provide a brief rationale for not notifying subjects.

9. DESCRIBE ANY FURTHER ACTION REQUIRED

10. PROVIDE ADDITIONAL COMMENTS OR INFORMATION TO ASSIST THE CBeIRB IN THE ASSESSMENT OF THIS SAE/I

As part of the reporting process, the PI will provide a rational for, and description of, changes to the protocol, consent or supporting documents that may be required as a result of the event. All revised documents will be submitted with the report.

Name of Principal Investigator:

_____

Signature of Principal Investigator (Name printed and signed) Date

Name of Immediate or Program Manager:

_____

Signature of Immediate or Program Manager (Name printed and signed) Date

Adverse Event Close Out Meeting/Report

Date:	
CBeIRB No:	**Project No.**
Project Title:	

Attendees:

Documentation Provided by PI:

Final Comments/Conditions of Approval:

Event determined to be _____ (level of seriousness) because:

Event was/was not related to the protocol because:

Final Action/Resolution:

Action:

This project is hereby approved for continuation by:

_____ The CBeIRB Chair (minor events only)
_____ The CBe Institutional Review Board
_____The CBeIRB Subcommittee as delegated by vote of the full CBeIRB.

The Adverse Event is considered closed.

David Wehrly, M.D..; M.P.H. (Name printed and signed) Date
CBeIRB Chair

Distribution: CBeIRB
PI
Sponsor
DOE-HQ