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RRC 003

Lifespan Institutional Recombinant DNA Committee (RDC)

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Approved by:

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Admin. Director, Office of Res. Administration

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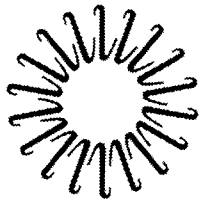
Sr. Vice President for Research

I. **Purpose:** The purpose of this policy and Procedure Manual is to define and describe the policies and procedures regulating the Lifespan Recombinant DNA Committee (RDC)

II. **Eligibility:** The entire research community of the Rhode Island Hospital, The Miriam Hospital, Emma Pendleton Bradley Hospital, Newport Hospital, collectively known as Lifespan for the purposes of this manual.

III. **Content:** The Manual is attached.



Lifespan

Recombinant DNA Committee (RDC)

Policy and Procedure Manual

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Recombinant DNA Committee

RDC

Section 1: Introduction

1.1 Purpose

The Recombinant DNA Committee (RDC) serves as the Institutional Biosafety Committee (IBC) for Lifespan. The purpose of the RDC is to assure that all recombinant DNA research conducted by the research community of Lifespan affiliates in Rhode Island is conducted according to the most recent version of the NIH Guidelines For Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines). Recombinant DNA research conducted at Women & Infants Hospital is also governed by this committee.

The purpose of this policy is to provide a mechanism for the review of proposed research activities involving recombinant DNA methods and materials. RDC review and approval is required before any project using recombinant DNA is initiated. This includes, but is not limited to: recombinant products, DNA probes, vector systems, and related material received from outside sources.

Review by the RDC includes evaluation for compliance and conformance with the NIH Guidelines; assessment of the containment levels required by the Guidelines; assessment of the facilities, procedures and practices; and consideration of the training and expertise of recombinant DNA personnel.

1.2 NIH Guidelines

The purpose of the *NIH Guidelines* is to specify practices for constructing and handling: (i) recombinant deoxyribonucleic acid (DNA) molecules, and (ii) organisms and viruses containing recombinant DNA molecules. The *NIH Guidelines* detail safety practices and containment procedures for basic and clinical research involving recombinant DNA, including the creation and use of organisms and viruses containing recombinant DNA.

In the context of the *NIH Guidelines*, recombinant DNA molecules are defined as either: (i) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) molecules that result from the replication of those described in (i) above.

1.3 Office of Biotechnology Activities (OBA) OBA

The NIH Office of Biotechnology Activities (OBA) promotes science, safety, and ethics in biotechnology through advancement of knowledge, enhancement of public understanding, and development of sound public policies. OBA accomplishes its mission through analysis, deliberation, and communication of scientific, medical, ethical, legal, and social issues. The Recombinant DNA Program within OBA promotes scientific advancement and safety in the conduct of basic and clinical recombinant DNA research. Institutional Biosafety Committees

(IBCs) provide institutional oversight of recombinant DNA research governed by OBA and the *NIH Guidelines*.

Section 2: Recombinant DNA Committee

2.1 Authority

Institutional Biosafety Committees (IBC's) derive their authority from the NIH. An institution must follow the *NIH Guidelines* if it receives any funding from the NIH for recombinant DNA research. Even if only one project of recombinant DNA research benefits from NIH support, all such projects conducted at or sponsored by that institution must comply with the *NIH Guidelines*.

The President and CEO of Lifespan delegates authority through the Institutional Official (IO) to appoint the chair(s) and members of the IBC. The Vice President for Research is the appointed IO at Lifespan. The IO is given the administrative and operational authority to commit institutional resources to ensure compliance with the *NIH Guidelines* and other requirements.

The IBC/s authority to review and approve protocols is independent of the IO, who may not overrule an IBC decision to withhold approval of a protocol. If the IBC approves a protocol, however, the Institution is not required or obligated to conduct the research activity. The Institution may also subject protocols to additional institutional review (e.g., department head, Biohazards and Lab Safety Committee, etc.) for initial and de novo reviews.

Lifespan has established an Institutional Biosafety Committee, the Recombinant DNA Committee, which is qualified through the experience and expertise of its members to oversee the Institution's program, facilities, and procedures.

The RDC Chairperson has the authority to immediately suspend <u>any</u> activity that endangers the facility or personnel safety. The suspension will be reported to the RDC for determination as to whether privileges will be reinstated or whether the suspension will be retained during the period of investigative review. A majority of members in attendance at a duly convened meeting at which quorum has been met are required to suspend research activities or research privileges. Suspensions will be reported in writing to NIH/OBA, the principal investigator, and project sponsor.

2.2 Composition

The Recombinant DNA Committee (RDC) is composed of scientists and community members who review all research proposals involving recombinant DNA experiments. The Committee shall consist of no less than 5 members recommended by their respective Department Head and appointed by the Institutional Official. At least two members shall not be affiliated with the institution and shall represent the interest of the surrounding community with respect to health and protection of the environment. Membership shall be qualified to meet the requirements for expertise as mandated by the *NIH Guidelines*. The Committee shall be known as the Lifespan Recombinant DNA Committee (RDC) and shall meet once a month on an as-needed basis. The

RDC will maintain certification of its membership with the NIH Office of Biotechnology Activities (OBA).

2.3 Responsibilities of the Committee

1. Review of recombinant DNA research protocols in regards to containment levels, laboratory facilities, and practices and procedures.
2. Develop policies and procedures to address safety precautions to be taken for the use of specific agents (e.g. ether) or activities (e.g. lab construction, relocation, or renovation) as needed.
3. Notify the principal investigator of the results of the committee's review
4. Ensure the research staff has adequate training and expertise to perform proposed research
5. Ensure that periodic inspections are conducted of laboratory facilities where recombinant DNA research is performed
6. Maintain an inventory of Biohazard Level – 2 (BL-2) or higher biological agents.
7. Serve as a resource for those investigators conducting research involving recombinant DNA.
8. Report any significant problems with or violations of the NIH guidelines and any significant research-related accidents or illnesses to the appropriate institutional official and NIH/Office of Biotechnology Activities (OBA) within 30 days.
9. The RDC shall report to the IO on an annual basis.
10. Upon request, [provide copies of RDC minutes and membership roster

2.4 Responsibilities of Principal Investigators

The Principal Investigator is responsible for:

1. Fully complying with the NIH Guidelines in conducting any recombinant DNA research
2. Registering all work involving all recombinant DNA agents or procedures with the RDC
3. Assuring that all review and approval requirements are fulfilled prior to initiating any new or modified research procedures
4. Ensuring that employees are adequately trained in safe work practices and techniques and in the procedures for dealing with accidental spills and personal exposure
5. Providing copies of the protocols and safety information sheets to laboratory staff
6. Assuring that necessary safety precautions and containment are maintained within the laboratory
7. Assure proper handling and disposal of biohazardous waste
8. Maintaining current Safety Certifications for the laboratory
9. Notifying the RDC of any significant changes in experimental protocol or location of the research
10. Providing information to the RDC as necessary

2.5 Conflict of Interest

No RDC member "may participate in the RDC review or approval of an activity in which that member has a conflicting interest, (e.g. is personally involved in the activity) except to provide information requested by the RDC."

For a complete description of the Lifespan policy and procedure regarding the registration and management of conflicts of interest please refer to the policy, ORA GEN 003. The Project Director, Principal Investigator (PD/PI), and any other person, regardless of title or position, who is **responsible** for the design, conduct or reporting of research that is conducted at Lifespan must report on their status of conflicts of interest at least annually. The Principal Investigators of each project are responsible for determining which people (e.g., co-investigators, collaborators, staff, trainees, consultants, etc.) meet the definition of "investigator" and are responsible for the filing of conflict of interest disclosures for each person. The Prinicpal Investigators are also responsible for ensuring that all members of the research team have completed the required COI training.

When they have reviewed a disclosure that may impact the review of a protocol by the RDC, the Lifespan Research Conflicts of Interest Committee promptly communicates to the RDC in writing. The RDC may participate in the development of a management plan of the conflict, if appropriate. In no case may research proceed on a project until the disclosed conflict is reviewed and resolved by the Lifespan Research Conflicts of Interest Committee.

For additional guidance, Lifespan's Corporate Compliance Policy #46, "Interaction with Industry Representatives (Pharmaceutical, Medical, Device and Medical Supply Industries)", Lifespan's Corporate Compliance Policy #09, "Conflicts of Interest" and Lifespan's Materials Management Policy #150, "Institutional Purchasing: Conflict of Interest Guidelines" further describe Lifespan's position on conflicts of interest.

An RDC member may also have professional or personal conflicts of interest. An RDC member is said to have a conflict of interest whenever that person, his or her spouse/partner, or dependent child falls under any one of the above conditions, or:

- Is an investigator or sub-investigator on the protocol.
- Is involved in a potentially competing research program.
- Access to funding or intellectual information may provide an unfair competitive advantage.
- A member's personal biases may interfere with his or her impartial judgment.
- Has identified him or herself for any other reason as having a conflict of interest.

RDC members and consultants will not participate in any RDC action taken, including the initial and continuing review of any project, in which the member has a conflict of interest, except to provide information requested by the RDC. RDC members are expected to self-identify conflicts of interest on the COI form prepared for each full board meeting.

If the investigator submitting a protocol believes that an RDC member has a potential conflict, the investigator may request that the member be excluded. The Chair (or in his/her absence, an Associate-Chair) will present the declared conflict and the Committee will determine whether a conflict exists. Should an RDC member declare involvement in any way in a research protocol under review by the RDC, or state a conflict of interest with the research protocol, then the member(s):

- Decline to serve as a primary reviewer of the application

- May remain in the meeting room to provide information requested by the RDC;
- Leave the meeting room for discussion and voting; and
- Are not counted towards quorum.

2.6 Quorum Requirements

Lifespan defines a "quorum" as more than half of the regular RDC voting members.

A protocol is approved only if a quorum is present, and if more than 50% of the quorum votes in favor of protocol approval. For reasons other than conflict of interest, abstentions from voting do not alter the quorum or change the number of votes required. For example: If the RDC has 15 voting members, at least 8 members must be present at a convened meeting to constitute a quorum and approval of a protocol would require a minimum of 5 of those 8 votes whether or not there were abstentions.

2.7 Public Access

RDC meetings are open to the public upon request. Meeting dates and contact information for the RDC Chairperson and Coordinator are posted on the RDC website.

Upon request, the institution shall make RDC meeting minutes available to the public in either paper or electronic format. Although not typically included in the minutes, any proprietary information contained therein would be redacted before release.

Questions or comments about the committee should be referred to the Coordinator or Chair who will bring this to the full committee at the next meeting to formulate a response. Any relevant comments will be forwarded to the OBA.

3.0 Procedure for Review of Recombinant DNA Research

The RDC review of all projects involving BL2 agents are conducted by way of a convened meeting. Occasionally, in the case of severe weather, meetings have been convened with some members participating by teleconference.

3.1 New Applications

All research protocols involving DNA research, as noted on the Request for Research Committee Review Application form, will be received by the Committee Coordinator in the Office of Research Administration and processed for review. Applications that are thought to be exempt will be forwarded to the Chair for review. If the research is determined to be exempt according to NIH Guidelines, the investigator will receive a notice of review status from the RDC Coordinator in the Research Protection Office. If the Chair determines that the research does not meet the definition of exempt research as described in the NIH Guidelines, the application will be processed for full board review by the convened committee. For applications that require full board review, the RDC Coordinator will assign two primary reviewers to review the protocol. If the designated reviewer feels he/she has a conflict of interest, or lacks sufficient expertise to review the protocol, an alternate reviewer may be requested. All RDC members will receive a copy of the application as well. The principal investigator or a representative who is

knowledgeable about the proposed research and competent to discuss the protocol will be asked to appear before the Committee at the next monthly meeting to present the research for review. After committee review is complete, the members will vote to approve, approve with modifications required to secure approval, or defer the proposal for further consideration at a later date. In some cases, the committee may feel the proposal should not be implemented and will so indicate.

Minutes of Committee meetings will be recorded, transcribed and maintained for inspection by the ORA Committees Coordinator. Notice of meeting schedule and application due dates will be posted on the Office of Research Administration website http://www.lifespan.org/research/dna/

3.2 Continuing Review

Those protocols that use BL-2 or higher microorganisms, as determined by the RDC, will be reviewed at least once annually and more frequently if the Committee feels it appropriate. The investigator will be required to complete a progress report which will be sent by the Office of Research Administration approximately 45 days before the report is due. Failure to submit a complete progress report will result in expiration of RDC approval of the research protocol until the report is filed, reviewed and approved for continuation. Failure to submit a complete progress report within 30 days of the expiration notice will result in termination of the project. Those protocols deemed exempt will not be required to undergo continuing review.

3.3 Changes to Protocol

It is the responsibility of the investigator to notify the Chair of the RDC in writing of any substantive intended change in the approved DNA research activity. For example, the addition of a new viral vector or a new cell line would be considered to be substantive changes which require review and approval by the RDC prior to initiation. The Committees Coordinator will receive all requests for revision. Such requests that do not appear to directly involve handling of recombinant DNA material, and do not appear to involve patient/personnel safety, will be forwarded to the Chair for expedited review. The Chair will review the requested change and determine whether it requires review by the full committee and/or any change in the original biosafety classification. The Chair has the authority to approve, approve with minor modification, or defer to the full board any request for revision to protocol. The Committee will be notified of all expedited reviews on the next agenda. Work on the amended protocol will not be undertaken until a letter of approval is issued by the Committee for the requested change.

3.4 Administrative Review

Should an investigator submit a DNA protocol to more than one agency, the initial application will be given a full review by the Committee. Subsequent submissions will be given an Administrative Review provided the investigator notifies the Chair in writing that the recombinant DNA portions of the subsequent application(s) are indistinguishable from the original, noting the date of the original approval. The Chair will review the application and approve the subsequent application(s) without requiring a review by the primary reviewers or full committee. An approval letter will be issued for each subsequent application. If the original application requires a continuing review then that review must be current (within the last 12 months).

Section 4: Reporting Incidents, Accidents and Violations

4.1 Accidental Exposure

Personnel exposed to recombinant DNA materials through splash, spills, needle sticks, inhalation, or other routes must report immediately to Employee and Occupational Health Services. If the incident occurs outside of routine business hours, then the individual must go to the Emergency Department. Principal Investigators are required to maintain Safety Information Sheets for the recombinant BL2 agents in use. These forms must be readily available to staff and include information regarding toxicity, infectivity, and replication competence. Personnel should bring a copy of the Safety Information Sheet for the agent to assist medical personnel who will provide treatment for the accidental exposure. The PI must report accidental exposures to the RDC as an unanticipated problem.

4.2 Types of incidents involving recombinant DNA that must be reported to the NIH OBA

Under Section IV-B-2-b-(7) of the *NIH Guidelines* states that IBCs should report "...any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses" to NIH OBA within 30 days. Appendix G of the *NIH Guidelines* specifies certain types of accidents that must be reported on a more expedited basis. According to Appendix G-II-B-2-k, spills or accidents in BL2 laboratories resulting in an overt exposure must be immediately reported to NIH OBA (as well as the IBC). According to Appendix G-II-C-2-q and Appendix G-II-D-2-k, spills or accidents occurring in high containment (BL3 or BL4) laboratories resulting in an overt or potential exposure must be immediately reported to NIH OBA (as well as the IBC, and Biological Safety Officer (BSO)).

Minor spills of low-risk agents not involving a breach of containment that were properly cleaned and decontaminated generally do not need to be reported. OBA staff should be consulted if IBCs, investigators, or other institutional staff are uncertain whether the nature or severity of the incident warrants reporting to OBA.

4.3 Responsibility to report

Reporting to NIH OBA is the responsibility of institution's, IBC Chair, BSOs, and PIs under Sections IV-B-1-j, IV-B-3-c-(2), and IV-B-7-a-(3), respectively. Institutions have the discretion to determine which party should make these reports, and one report for each incident or set of information is generally sufficient.

4.4 Information to be included within an incident report

Incident reports should include sufficient information to allow for an understanding of the nature and consequences of the incident, as well as its cause. A detailed report should also include the measures that the institution took in response to mitigate the problem and to preclude its reoccurrence.

Mail :
Office of Biotechnology Activities
National Institutes of Health
6705 Rockledge Dr., Suite 750
Bethesda, MD 20892-7985
Phone: (301)-496-9838
Fax: (301) 496-9839

Section 5: Special Topics

5.1 Review of Research Utilizing Gene Transfer Technology

The RDC recognizes that research utilizing gene transfer technology in human subjects requires additional considerations for review and monitoring. Research involving human subjects treated with gene transfer methods will be reviewed by both the RDC and the Institutional Review Board (IRB). RDC responsibility for the review of gene transfer technology protocols includes, but is not limited to, safety and efficacy of the virus in human subjects and occupational safety of research and hospital staff.

All human gene transfer studies should if appropriate, be reviewed and approved by the Recombinant DNA Advisory Committee (RAC) at the NIH Office of Biotechnology (OBA) prior to initiation. All serious adverse events must also be reported to RAC.

The RDC requires a written report on: (1) any serious adverse event that is both unexpected and associated with the use of a gene transfer product; and (2) any finding from tests in laboratory animals that suggest a significant risk for human research participants. Furthermore, all other relevant committees and agencies must be included in the appropriate content, format and time frame for each committee or agency respectively. The time-frame for reporting a verbal report to all agencies is within 24 hours of event with a written report submitted by 48 hours from onset of event. Any study will go on automatic hold at time of serious adverse event until fully investigated and cleared by all relevant agencies and committees.

The RDC encourages the use of the GeMCRIS database for reporting adverse events on human gene transfer trials. For more information regarding GeMCRIS please visit: http://oba.od.nih.gov/rdna/adverse_event_oba.html

The RDC primary reviewers assigned to examine the application with regard to recombinant DNA issues will be available to the IRB as scientific consultants. The RDC reviewers or the Chair will be available to present the recombinant DNA perspective to the IRB upon request. In return, the RDC will request that the IRB primary reviewers or designates be available to advise the RDC of human subjects protection concerns. Joint review will be coordinated by the Committee Coordinator. Adverse events involving research participants involved in gene transfer technology protocols will be reviewed by both the IRB and the RDC, in accordance with IRB adverse event reporting policy.

5.2 Use of recombinant DNA BL2 Agents in Animals

All projects involving both recombinant DNA and animals will be designated BL-1 or BL-2 by the Recombinant DNA Committee at the time of initial review.

Requirement for BL-1 Agents:

Work involving cells previously modified in culture by the introduction of replication incompetent retroviral vectors would be considered animal level BL-1, as described in NIH Guidelines for Research Involving Recombinant DNA (NIH Guidelines), Section III-D-4-a.

Standard CRF housing and husbandry procedures will be followed for animals on BL-1 protocols.

Requirements for BL-2 containment:
Genetic engineering has made viral vectors safer by designing them to be replication defective outside of specialized packaging cell lines. This greatly limits the possibility of generating replication competent virus which poses a higher risk of infection.

Replication defective viral vectors are handled at BL-2 in the laboratory because of their potential to enter human cells, deliver genetic material, and elicit an immune response. Viral vectors in this category include adenovirus, adeno-associated virus, lentivirus, and various retroviruses.

Administration of viral vectors in animals likewise must be performed in an animal BL-2 animal holding room. Data has shown that shedding (excretion) of virus particles significantly decreases after 72 hours, post inoculation.

The Recombinant DNA Committee (RDC) requires that animal work done by personnel from a laboratory that is directly administering viral vectors or biohazard level 2 agents be conducted under NIH precautions for Animal Biosafety Level 2 (BL-2). Rodents involved in this research will be housed in an appropriate animal room of the Central Animal Facility (CAF). The animal handling and husbandry procedures for Animal Biosafety Level 2 (ABLS2) are described in the CAF Policy and Procedure Manual.

5.3 Inspection of Laboratory Facilities

The Safety Officer is charged with performing periodic inspections to ensure that laboratory standards are rigorously followed. Any significant problems relating to recombinant DNA research that are encountered as a result of these inspections should be promptly reported to the RDC.
In conjunction with the laboratory inspections conducted by the chemical hygiene officer and the Biohazards and Laboratory Safety Committee (BLSC), the RDC will ensure that annual inspections are conducted in those laboratories performing recombinant DNA research to ensure that laboratory standards are rigorously followed. The RDC will maintain and update a list of laboratories that conduct recombinant DNA research.

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5.4 Inventory of Material Transfer Agreements and Distribution of BL-2 (and Higher) Biological Agents

The *NIH Guidelines* for Recombinant DNA Research requires that the RDC monitor the use of vectors derived from viruses and/or cell lines with incorporated viral sequences. To comply with this requirement, the Office of Research Administration (ORA) will maintain a file of material transfer agreements. The investigator is required to maintain an inventory of BL-2 agents that are used within the lab. The inventory will be updated at the time of annual laboratory inspection and the investigator will be responsible for final accountability of the inventory at the time he/she leaves the institution.

5.5 Waste disposal of recombinant DNA materials

Recombinant DNA materials must be disposed of by following hospital disposal regulations. All sharps, including pipet tips, must be disposed of in sharps containers. Lab waste must be disposed of in red bag waste container. Liquid waste from cultures must be treated with the addition of stabilized sodium hypochlorite such as Dispatch, or freshly prepared bleach to a final concentration of 10% and allowed to sit for at least 5 minutes before disposal down the sink.

5.6 Screening for Replication Competent Viruses

Recombination events or contamination with wild type viruses can result in the production of replication competent virus (RCV) in a population of replication deficient viral stocks. The Recombinant DNA committee requires testing for the presence of RCV in viral stocks and the method of testing must be indicated in the appropriate section of the application. For each category of viral vector, (e.g.: adenoviral viral, retroviral vector or lentivirus derived vector) refer to Section 7.3 for links to the recommended procedures for the detection of RCV.

Section 6: Education and Training

Principal Investigators (PIs) are responsible for providing specific training to their staff regarding the BL-2 agents to be used in the lab. PIs must maintain documentation of this training, and provide it with all new and continuing applications. Additionally, the RDC has created an on-line training program that should be completed by all investigators and research staff in the laboratory before initiating recombinant DNA work. In addition the RDC will on an as-needed basis, provide interested members of the research community with additional educational and training information necessary for the investigator to maintain a safe laboratory environment and to ensure research conducted in the laboratory is within the *NIH Guidelines*. The Committee will serve as a resource mechanism as well as a review mechanism.

Section 7: Resources

7.1 RDC Member Roster

Please contact the Committee Coordinator for the most recent list of RDC members (jpoore@lifespan.org, 444-2093)

7.2 List of Lifespan Investigators Using Recombinant DNA Methodology

Please contact the Committee Coordinator for the most recent list of investigators (jpoore@lifespan.org, 444-2093)

7.3 FORMS: Please be sure to download the most recent version of the forms for all submissions

- RDC Application
- Progress Report
- BL-2 Employee Training
- Safety Information Sheets for Recombinant DNA Materials
  - Viral:
  - Non-viral

- **Recommended Testing Procedures for Adenoviral Vectors and Replication Competent Virus - Annual Requirement for Biosafety 2 Approval**
  - **Adenovirus**
  - **Retrovirus**
- **S.O.P. for Handling and Storage of Human Subject Study Reagents Utilizing Recombinant DNA in Viral Vectors**
  - **guidance**

7.4 Safety Resources

Please refer to the Environmental Safety Department website for additional information.