Saint Louis University

IBC Manual for Recombinant DNA Work

Index

OVERVIEW of EXPERIMENTS COVERED by NIH GUIDELINES for RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

1. **Purpose of the NIH Guidelines:** The purpose of the *NIH Guidelines* is to specify practices for constructing and handling:
   (i) recombinant deoxyribonucleic acid (DNA) molecules
   (ii) organisms and viruses containing recombinant DNA molecules

2. **Compliance with the NIH Guidelines:** As a condition for NIH funding of recombinant DNA research, Saint Louis University (SLU) will ensure that such research conducted at or sponsored by the institution, irrespective of the source of funding, shall comply with the *NIH Guidelines*.

   All NIH-funded and non NIH-funded projects involving recombinant DNA techniques must comply with the *NIH Guidelines*.
   Non-compliance may result in:
   (i) suspension, limitation, or termination of financial assistance for the noncompliant NIH-funded research project and of NIH funds for other recombinant DNA research at SLU
   (ii) a requirement for prior NIH approval of any or all recombinant DNA projects at SLU.

DEFINITIONS

Institution: Any public or private entity (including Federal, state, and local government agencies).

Office of Biotechnology Activities (OBA): The office within the NIH that is responsible for: (i) reviewing and coordinating all activities relating to the *NIH Guidelines*, and (ii) performing other duties as defined in Section IV-C-3, *Office of Biotechnology Activities (OBA)*.

Recombinant DNA Advisory Committee (RAC): The public advisory committee that advises the Department of Health and Human Services (DHHS) Secretary, the DHHS Assistant Secretary for Health, and the NIH Director concerning recombinant DNA research. The RAC shall be constituted as specified in Section IV-C-2, *Recombinant DNA Advisory Committee (RAC)*.

NIH Director: The Director of the National Institutes of Health, or any other officer or employee of NIH to whom authority has been delegated.

Enrollment: The process of obtaining informed consent from a potential research participant, or a designated legal guardian of the participant, to undergo a test or procedure associated with the gene transfer experiment.

Serious Adverse Event (SAE): Any event occurring at any dose that results in any of the following outcomes: death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization also may be considered a serious adverse event when, upon the basis of appropriate medical judgment, they may jeopardize the human gene transfer research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Adverse Event (AE): Event that is "Associated with the use of a gene transfer product" when there is a reasonable possibility that the event may have been caused by the use of that product.

Unexpected Serious Adverse Event: Any serious adverse event for which the specificity or severity is not consistent with the risk information available in the current investigator's brochure.

Definition of Recombinant DNA Molecules: 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.

Synthetic DNA segments which are likely to yield a potentially harmful polynucleotide or polypeptide (e.g., a toxin or a pharmacologically active agent) are considered as equivalent to their natural DNA counterpart. If the synthetic DNA segment is not expressed *in vivo* as a biologically active polynucleotide or polypeptide product, it is exempt from the *NIH Guidelines*.

Genomic DNA of plants and bacteria that have acquired a transposable element, even if the latter was donated from a recombinant vector no longer present, are not subject to the *NIH Guidelines* unless the transposon itself contains recombinant DNA.

Laboratory Scale Research: Less than 10 liters.

Large Scale Research: Greater than 10 liters.

A: RESPONSE PLANS

Introduction

Advance preparation for spills, personnel exposures, and other accidents involving organisms containing Recombinant DNA is essential. These procedures are developed to assist the Principal Investigator (PI) to respond to spills involving organisms containing Recombinant DNA in the laboratory. These procedures address minor spills involving Risk Group (RG) 1 and 2 organisms – as defined within the NIH Guidelines - containing recombinant DNA. In the event of a large spill or a spill involving an organism that is classified as a Risk Group 3 recombinant DNA pathogen, contact the Saint Louis University Emergency Dispatch at 977-3000 to page the Office of Environmental Safety and Services for assistance with decontamination and cleanup. In all cases the principal investigator is responsible for maintaining an adequate supply of a chemical disinfectant effective against the microorganisms being investigated.

Disinfectant must show efficacy against the pathogens being manipulated by the PI.

1. SPILLS

RG 1 and RG2 organisms containing Recombinant DNA spilled within a Biological Safety Cabinet

A spill involving organisms containing Recombinant DNA confined to the interior of a biological safety cabinet generally presents little or no hazard to personnel in the area. However, decontamination procedures should be initiated at once while the cabinet ventilation system continues to operate. This is to prevent the escape of the contaminants from the cabinet.

All spills within biological safety cabinets involving organisms containing recombinant DNA will be contained, decontaminated, and area cleaned consistent with the recommendations for that particular organism as stated within the Institutional Biosafety Committee (IBC) approved application.

The following is a general procedure for cleaning such a spill:

A. Maintain cabinet ventilation.
B. Notify others in the laboratory.
C. Wear disposable gloves, a lab coat, and mask with eye protection.
D. Spray or wipe walls, work surfaces, and equipment with appropriate disinfectant. A disinfectant with detergent has the advantage of detergent activity that will help clean the surfaces by removing both organic material and microorganisms.
E. Use sufficient disinfectant to ensure that drain pans and catch basins below the work surface contact the disinfectant. Lift the front exhaust grill and tray. Wipe all surfaces. Wipe the catch basin and drain the disinfectant into a container.
F. Observe the recommended contact time for the disinfectant.
G. Discard the used disinfectant in sink basin. Place disposable PPE and other disposable cleanup materials into an autoclave bag and autoclave.
H. Notify the principal investigator and the Office of Environmental Safety and Services at 977-3000.

RG1 and RG2 organisms containing Recombinant DNA Spilled in the Open Laboratory

If organisms containing Recombinant DNA are spilled in the open laboratory, take the following actions:

A. Isolate immediate spill zone and notify others in the laboratory.
B. Remove any sharps materials using tongs, tweezers, or other hands-free technique and place contaminated material within a sharps container.
C. Place paper towel on spill and saturate with a disinfectant known to be efficacious against the organism containing rDNA. Allow contact time consistent with product label.
D. Place all potentially contaminated materials within a biological waste container.
E. If clothing is known to be contaminated, carefully remove it, folding the contaminated area inward. Place the clothing into an autoclave bag.
F. Wash arms, face, and hands with soap and water.
G. Notify the principal investigator and the Office of Environmental Safety and Services via Public Safety Dispatch at 977-3000 informing them of the actions taken to contain, disinfect and clean the spill.

RG1 and RG2 organisms containing Recombinant DNA Spilled in a Centrifuge

Spills in centrifuges have the potential for generating large volumes of aerosols of Recombinant DNA organisms. When the operator becomes aware that a spill has occurred, the following action shall be taken:

A. If not already off, turn off the centrifuge and allow for approximately 30 minutes for the aerosols to settle.
B. Notify others in the laboratory.
C. Laboratory staff will don disposable gloves and other protective clothing as necessary.
D. Decontaminate with an appropriate disinfectant by saturating all centrifuge surfaces.
E. Notify the principal investigator and the Office of Environmental Safety and Services via Public Safety Dispatch at 977-3000 informing them of the actions taken to contain, disinfect and clean the spill.

2. PERSONNEL EXPOSURES INVOLVING ORGANISMS CONTAINING RECOMBINANT DNA

This information is in accordance with the Saint Louis University Exposure Control Plan, updated annually. Please note that procedures for exposure to blood/body fluids are under separate policy.

General

Any direct contact without barrier protection to organisms containing recombinant DNA in a laboratory facility is considered an exposure. Percutaneous injuries may include a needlestick or a cut with a sharp object from objects that have manipulated materials containing recombinant DNA.

Recombinant DNA Exposure

Employee Health is the designated provider of care for work related injury/exposure to recombinant DNA for SLU employees.
The injured employee, employee supervisor, Environmental Safety and Services, Employee Health, Risk Management and Human Resources will follow the procedures outlined in Saint Louis University Worker's Compensation Policy.

1. Immediately after an injury:
   -The employee exits the work area where the incident occurred according to department/project procedure.
   -The employee does any initial wound care measures as outlined in the project protocol.
   -The employee reports **immediately** to the supervisor. Together the supervisor and the injured employee complete an Employee Report of Injury.
   -The employee is escorted/sent to Employee Health.
   -If the injury occurs after normal business hours, the employee is escorted/sent to Saint Louis University Hospital Emergency Room. The Emergency Room triage nurse (314-577-8777) should be advised in advance before the injured employee arrives. This is to allow proper isolation from the time of arrival if isolation is appropriate.
   -If the injury is severe, the employee is escorted/sent to Saint Louis University Hospital Emergency Room. The Emergency Room triage nurse (314-577-8777) should be advised in advance before the injured employee arrives. This is to allow proper isolation from the time of arrival if isolation is appropriate.
   -If the initial treatment is in the Emergency Room, the employee must follow up at Employee Health on the next business day.
2. Employee Health will perform initial evaluation and treatment.
3. Current vaccination status is documented via the Employee Health file and employee report.
4. Digital photography is available at Employee Health to document lesions.
5. Baseline serum and whole blood samples may be obtained if required by the IBC. Other agent specific samples may be obtained based on circumstances.
6. Infectious Disease will be notified and consulted if necessary. This may be done through Employee Health or through the SLUHospital Emergency Room. This may be one or all of the following:
   -Attending on service with the consult service
   -Infection Control officer or designee.
7. Laboratory consultation is available through the director of the Microbiology lab or Virology lab.
8. CDC consultation will be sought as necessary.
9. Consult of medical experts from NIH/OBA will be sought as necessary.
10. Principal investigator (or designee) will be notified.
11. Responsible Officer (or designee) will be notified.
12. Director of Environmental Safety and Services will be notified.
13. Health Departments will be notified as required including City of St. Louis, Saint Louis County, and State of Missouri.
14. CDC will be notified as required.
15. The Biological Safety Officer in conjunction with Employee Health staff will provide

counseling regarding recombinant DNA exposure to the exposed employee.

16. The injured employee will be provided a certificate of fitness outlining the return to work status.
17. Return to work status:
    -The employee immediately reports back to the supervisor (unless the injury is severe) with the Certificate of Fitness.
    -The supervisor notes the work status including any restriction on the certificate of fitness and follows the appropriate procedure outlined in the Saint Louis University Worker's Compensation Policy.
    -Questions regarding the work restrictions are to be discussed with Employee Health by the injured employee or by the supervisor.
    -Questions regarding implementation of the work restrictions are to be addressed to the supervisor. If the supervisor is not able to address the employee's concerns, the Department of Human Resources will assist in accommodating the work restrictions.
18. The injured employee will be provided all instructions regarding follow up. This may include:
    - Activity restrictions
    - Guidelines for follow up surveillance including flow sheet (temperature, symptoms, etc)
    - Recommendations for household (family) contact precautions
    - Instructions for medications and other medical treatment
    - Instructions on after-hours care
    - Additional personal protective equipment use (PPE will also be issued to the injured employee)
19. Employee Assistance Program (EAP) services are available if needed.
20. The injured employee must comply with treatment prescribed by the Employee Health physician.
21. Worker compensation benefits will be managed through the office of Risk Management and the third party administrator.

Report/Investigation of Exposure Incident

Employee Health (268-5499) and/or the Biological Safety Officer (977-6888) will review the circumstances of all exposure incidents to determine:

A. Engineering controls in use at the time
B. Work practices followed
C. Description of the device being used (including type and brand if applicable)
D. Personal protective equipment that was used at the time of the exposure incident
E. Location of the incident
F. Procedure being performed when the incident occurred
G. Employee documentation and training
    1. SLU Risk Management (977-3952) will record all OSHA recordable injuries in the OSHA300 Log.
    2. The Biological Safety Officer, in conjunction with the Institutional Biosafety Committee (IBC) will amend the Response Plan for Incidents Involving Recombinant DNA if it is determined that revisions need to be made.
    3. Employee training or re-training will be completed and documented on a case-by-case basis.

3. ALL OTHER INCIDENTS INVOLVING RECOMBINANT DNA

Response for Other Accidents Involving recombinant DNA

For any other incident in the laboratory involving material containing Recombinant DNA, contact Saint Louis University's Office of Environmental Safety and Services at 977-3000.

B: INCIDENT REPORTING

Requirement

The *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) states that "...any **significant** problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses" must be reported to NIH OBA within 30 days. **Please note: The Principal Investigator is ultimately responsible for assuring that incident reporting is completed and that it is consistent with the requirements of the NIH Guidelines and consistent with the recommendations of the Saint Louis University IBC.**

1. REPORTING THRESHOLDS*

Certain types of incidents must be reported on a more expedited basis. Spills or accidents in BSL-2 laboratories resulting in an overt exposure must be immediately reported to NIH OBA. Spills or accidents occurring in high containment (BSL-3) laboratories resulting in an overt or potential exposure must be immediately reported to NIH OBA.

2. REPORTING INSTRUCTIONS:

The following document serves as a guide for reporting incidents involving recombinant DNA. Please answer the following questions regarding incident.

Does this incident involve research subject to the *NIH Guidelines*?	□ YES □ NO If no, this incident does not have to be reported to OBA
Institution name:	
Date of Report:	
Reporter name and position:	
Reporter telephone:	
Reporter email:	
Date of incident:	
Name of principal investigator:	
Is this an NIH funded project?	
If yes, please provide:	NIH grant or contract number:
	NIH funding institute or center:
	NIH program officer contact information (name, email):
What was the **nature** of the incident?	□ Personnel exposure:
	□ Spill
	□ Loss of containment
	□ Loss of transgenic animal
	□ Failure to obtain IBC approval
	□ Failure to follow approved containment conditions
	□ Other – please describe:
Did the Institutional Biosafety	□ YES □ NO

Committee (IBC) approve this research?	If yes, on what date?
If yes, please provide:	Approval Date:
	Approved biosafety level for the research:
	Additional approval requirements:
What section(s) of the *NIH Guidelines* is the research subject to?	
Has a report of this incident been made to other federal or local agencies? If so, please indicate by checking the appropriate box.	□ CDC □ USDA □ FDA □ EPA □ OSHA □ Research Funding Agency/Sponsor: (name)_____ □ State/Local Public Health □ Federal/State/Local Law Enforcement Other – please describe:

Please provide a narrative of the incident including a timeline of events. The incident should be described in sufficient detail to allow for an understanding of the nature and consequences of the incident. **Include the following information as applicable.**

A description of:

- The recombinant agent or material involved.
- The incident/violation location (e.g. laboratory biosafety level, vivarium, non-laboratory space).
- Who was involved in the incident/violation, including others present at the location? **Note – please do not identify individuals by name. Provide only position titles (e.g., graduate student, post doc, animal care worker, facility maintenance worker).**
- Actions taken immediately following the incident/violation, and by whom, to limit any health or environmental consequences of the event.
- The training received by the individual(s) involved and the date(s) the training was conducted.
- The institutional or laboratory standard operating procedures (SOPs) for the research and whether there was any deviation from these SOPS at the time of the incident/violation.
- Any deviation from the IBC approved containment level or other IBC approval conditions at the time of the incident/violation.
- The personal protective equipment in use at the time of the incident/violation.
- The occupational health requirements for laboratory personnel involved in the research.
- Any medical advice/treatment/surveillance provided or recommended after the incident.
- Any injury or illness associated with the incident.

- Medical surveillance results (if not available at the time of initial report please indicate when results will be available).
- Equipment failures.

DESCRIPTION OF INCIDENT: (use additional space as necessary)

Has the IBC reviewed this incident?	□ YES □ NO If yes, please provide a copy of the minutes of the IBC meeting in which the incident was reviewed.
Has a root cause for this incident been identified?	□ YES □ NO If yes, please describe:
Describe the measures taken by the institution to mitigate any problems identified. For measures identified by not yet taken, please include a timeline for their implementation: (use additional space as necessary).	

- Please provide copies of any documents referenced in this report.
- Additional information may be requested by OBA after review of this report depending on the nature of the incident.

3. NIH/OBA – Frequently Asked Questions Guide:

***How serious must a problem be to warrant reporting to OBA?**
Any spill or accident involving recombinant DNA research of the nature described above or that otherwise leads to personal injury or illness or to a breach of containment must be reported to OBA. These kinds of events might include skin punctures with needles containing recombinant DNA, the escape or improper disposition of a transgenic animal, or spills of high-risk recombinant materials occurring outside of a biosafety cabinet. Failure to adhere to the containment and biosafety practices articulated in the *NIH Guidelines* must also be reported to OBA.

Minor spills of low-risk agents (RG1 and RG2) not involving a breach of containment that were properly cleaned and decontaminated generally do not need to be reported. OBA should be consulted if the Institutional Biosafety Committee (IBC), investigator, or other institutional staff is uncertain whether the nature or severity of the incident warrants reporting; OBA can assist in making this determination.

Who is responsible for reporting incidents involving recombinant DNA to NIH OBA?
Under the *NIH Guidelines* incident reporting is articulated as a responsibility of the Institution, IBC, Biological Safety Officer, and Principal Investigator. Institutions have the discretion to determine which party should make these reports, and one report or set of information for each incident is generally sufficient.

What information should incident reports include?
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.

What other information needs to be provided?
Depending on the severity of the incident, OBA staff may request the IBC meeting minutes documenting approval conditions for the research, minutes of IBC meetings where the incident was reviewed, policies in place at the time the incident occurred, or any revised policies prepared in response to the incident. Training records for the personnel involved in the incident may also be requested.

What does OBA do with this information?
OBA staff review incident reports to assess whether the institutional response was sufficient. Depending on the adequacy of the institutional response, OBA may ask the institution to take additional measures as appropriate to promote safety and compliance with the *NIH Guidelines*.

Do adverse events experienced by participants in human gene transfer trials fall under this incident reporting requirement?
No, adverse events in human gene transfer trials are subject to a separate set of reporting requirements. These are found in Appendices M-1-C-3 and M-1-C-4 of the *NIH Guidelines*. Serious adverse events that are unexpected and possibly associated with the gene transfer product should be reported to OBA within 15 calendar days of sponsor notification, unless they are fatal or life threatening, in which case they should be reported within 7 calendar days. Other serious

adverse events should be reported to OBA as part of the Principal Investigator's annual report to OBA.

To report an incident involving exposure, contact OBA via:

Kathryn Harris, Ph.D., RBP
Senior Outreach and Education Specialist
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892
Phone: 301-496-9838
Fax: 301-496-9839
Email: harriskath@od.nih.gov

C: SERIOUS ADVERSE EVENT REPORTING

Requirement
NIH Guidelines specify the reporting requirements necessary for the initiation of clinical investigation, additional clinical trial sites, annual reporting and serious adverse event reporting (Appendix M-I-C)

NIH Guidelines apply to all NIH-funded projects involving recombinant DNA techniques as well as to all non-NIH funded research conducted at or sponsored by an institution that receives NIH funds for projects involving such techniques.

The scope and timing of safety reports to the NIH were recently modified to be harmonized with those of the FDA so that the same information can be reported to both agencies on the same schedule. (http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-02-052.html.)

1. SERIOUS ADVERSE EVENT

Serious Adverse Event reporting applies to all site personnel involved in the administration / coordination of sites for gene therapy protocols.

Responsibility of Principal Investigator: The Principal Investigators must submit, in accordance with this section, Appendix M-I-C-4-a and Appendix M-I-C-4-b, a written report on: (1) any serious adverse event that is both unexpected and associated with the use of the gene transfer product (i.e., there is reasonable possibility that the event may have been caused by the use of the product; investigators should not await definitive proof of association before reporting such events); and (2) any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity. The report must be clearly labeled as a "Safety Report" and must be submitted to the NIH Office of Biotechnology Activities (NIH OBA) and to the local Institutional Biosafety Committee within the timeframes set forth in Appendix M-I-C-4-b.

Principal Investigators should adhere to any other serious adverse event reporting requirements in accordance with federal regulations, state laws, and local institutional policies and procedures, as applicable.

Principal Investigators may delegate to another party, such as a corporate sponsor, the reporting functions set forth in Appendix M, with written notification to the NIH OBA of the delegation and of the name(s), address, telephone and fax numbers of the contact(s). The Principal Investigator is responsible for ensuring that the reporting requirements are fulfilled and will be held accountable for any reporting lapses.

The three alternative mechanisms for reporting serious adverse events to the NIH OBA are: by e-mail to oba@od.nih.gov; by fax to 301-496-9839; or by mail to the Office of Biotechnology Activities, National Institutes of Health, MSC 7985, 6705 Rockledge Drive, Suite 750, Bethesda, Maryland 20892-7985.

Safety Reporting Content and Format: The serious adverse event report must include, but need not be limited to:

(1) Date of the event;

(2) Designation of the report as an initial report or a follow-up report, identification of all safety reports previously filed for the clinical protocol concerning a similar adverse event, and an analysis of the significance of the adverse event in light of previous similar reports;

(3) Clinical site;

(4) Name of Principal Investigator;

(5) NIH Protocol number;

(6) FDA's Investigational New Drug (IND) Application number;

(7) Vector type , e.g., adenovirus;

(8) Vector subtype, e.g., type 5, relevant deletions;

(9) Gene delivery method, e.g., *in vivo, ex vivo* transduction;

(10) Route of administration, e.g., intratumoral, intravenous;

(11) Dosing schedule;

(12) A complete description of the event;

(13) Relevant clinical observations;

(14) Relevant clinical history;

(15) Relevant tests that were or are planned to be conducted;

(16) Date of any treatment of the event; and

(17) The suspected cause of the event.

These items may be reported by using the recommended Adverse Event Reporting Template available on NIH OBA's web site at: http://oba.od.nih.gov/oba/rac/Adverse_Event_Template.pdf, the FDA MedWatch forms, or other means provided that all of the above elements are specifically included.

Reports from laboratory animal studies as delineated in Appendix M-I-C-4 must be submitted in a narrative format.

Safety Reporting Time frames for Expedited Reports: Any serious adverse event that is fatal or life-threatening, that is unexpected, and associated with the use of the gene transfer product must be reported to the NIH OBA as soon as possible, but not later than 7 calendar

days after the sponsor's initial receipt of the information (i.e., at the same time the event must be reported to the FDA).

Serious adverse events that are unexpected and associated with the use of the gene transfer product, but are not fatal or life-threatening, must be reported to the NIH OBA as soon as possible, but not later than 15 calendar days after the sponsor's initial receipt of the information (i.e., at the same time the event must be reported to the FDA).

Changes in this schedule are permitted only where, under the FDA IND regulations [21 CFR 312(c)(3)], changes in this reporting schedule have been approved by the FDA and are reflected in the protocol.

If, after further evaluation, an adverse event initially considered not to be associated with the use of the gene transfer product is subsequently determined to be associated, then the event must be reported to the NIH OBA within 15 days of the determination.

Relevant additional clinical and laboratory data may become available following the initial serious adverse event report. Any follow-up information relevant to a serious adverse event must be reported within 15 calendar days of the sponsor's receipt of the information. If a serious adverse event occurs after the end of a clinical trial and is determined to be associated with the use of the gene transfer product, that event shall be reported to the NIH OBA within 15 calendar days of the determination.

Any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity must be reported as soon as possible, but not later than 15 calendar days after the sponsor's initial receipt of the information (i.e., at the same time the event must be reported to the FDA).

D: HEALTH SURVEILLANCE IN RECOMBINANT DNA RESEARCH

1. HEALTH SURVEILLANCE REQUIREMENTS

The institution shall establish and maintain a health surveillance program for personnel engaged in **large-scale research** or **production activities** involving viable organisms containing recombinant DNA molecules **which require BL3 containment at the laboratory scale**.

The IBC will determine the necessity for health surveillance of personnel involved in connection with individual recombinant DNA projects.

Employee Health will provide occupational health services related to IBC recommended medical surveillance.

Certain medical conditions may place a laboratory worker at increased risk in any endeavor where infectious agents are handled. Examples cited in the *Laboratory Safety Monograph* include gastrointestinal disorders and treatment with steroids, immunosuppressive drugs, or antibiotics. Workers with such disorders or treatment should be evaluated to determine whether they should be engaged in research with potentially hazardous organisms during their treatment or illness. It is the responsibility of the PI to ensure that employees known to be at increased risk are evaluated.

2. PROTOCOL REVIEW

Employee Health will work with the Biosafety Officer and principal investigators to review research protocols to determine the need for medical surveillance. Each review is designed to determine the following information:

a. Gain an understanding of risks to workers
b. Provide clear procedures for reporting incidents and exposures
c. Identify involved personnel

3. SERUM COLLECTION PROGRAM

The IBC will determine if serum from laboratory workers engaged in a specific protocol involving organisms containing recombinant DNA will be collected and maintained.

If directed by the IBC, the principal investigator will arrange with Employee Health to establish a schedule to obtain serum specimens from each laboratory worker prior to the time that work with organisms containing recombinant DNA is initiated. and will arrange with Employee Health to establish a schedule to obtain serum specimens from each laboratory worker at periodic intervals as designated by the IBC.
If directed by the IBC, the principal investigator will arrange with Employee Health to establish a schedule to obtain serum specimens from each laboratory worker prior to termination of employment.
If directed by the IBC, serum specimens will be obtained immediately following an overt exposure and at an appropriate time after such an exposure.

4. IMMUNIZATIONS

Immunization is generally recommended for laboratory workers who will be engaged in research with infectious organisms containing recombinant DNA for which an effective vaccine is available. The IBC may require prior immunization as a condition for working on a project involving organisms containing recombinant DNA. Where immunizations are required, evidence of antibody response may be demonstrated if available before a worker begins to work with infectious organisms containing recombinant DNA.

Employee Health must be notified which immunizations need to be addressed in each individual worker in advance of the assessment in order for this to be accomplished at the time of pre-placement.

5. REPORTING AND INVESTIGATING ACCIDENTS AND ILLNESSES

a. ILLNESSES

If an organism containing recombinant DNA were to acquire the capacity to infect and cause disease in man, the first evidence of this potential may be demonstrated by a laboratory-acquired infection. For this reason it is important to investigate any serious, unusual, or extended illness of a laboratory worker engaged in research involving organisms containing recombinant DNA or any accident that involves inoculation of organisms containing recombinant DNA molecules through the skin, by ingestion, or probable inhalation. A finding that infection is associated with research with organisms containing recombinant DNA will prompt immediate reporting to NIH/OBA and initiation of additional precautions to protect workers and the general public if necessary.
Laboratory workers are encouraged to report all major, unusual or extended illnesses to Employee Health. These cases will be reviewed for possible occupational origin and recorded for future reference.

b. ACCIDENTS

Prompt reporting of accidents involving overt exposures to organisms containing recombinant DNA is essential. The laboratory worker involved with such an occurrence will notify the principal investigator and the Biological Safety Officer immediately. The procedures outlined in section A.Reponse Plans 2. Personnel Exposures are to be followed.

Reported first-aid and lost-time occupational accidents, as well as accidents without personal injury but which result in exposure of the worker to a potential hazardous organism containing recombinant DNA are noted in the Employee Health record with the result of examinations deemed appropriate by the physician at that time.
Reporting procedures outlined in section A. Reponse Plans 2. Personnel Exposures are to be followed.

6. MEDICAL EXAMINATIONS

It is impossible to make specific recommendations concerning the need for either pre-assignment or periodic medical examinations for laboratory workers engaged in research involving organisms containing recombinant DNA. Such recommendations must by

determined on a case by case basis and will depend on the assessed hazards of the project and the individual needs of the laboratory worker.

Certain medical conditions may place a laboratory worker at increased risk. For example, laboratory workers who are undergoing treatment with steroids, immunosuppressive drugs or antibiotics, or are suffering from illness, should have a medical evaluation to determine whether they should be engaged in research with potentially hazardous organisms during the time of their treatment or illness.

Pregnant women can request counseling as to the advisability of working in areas where the potential for exposure to potentially hazardous organisms is present. This is done by contacting Employee Health.

Any changes in the health status of a laboratory worker, who is engaged in research with potentially hazardous organisms, should be brought to the attention of Employee Health. This will ensure the best appropriate guidance.

a. Pre-placement

Where the potential for laboratory-acquired illness is known to exist, pre-placement assessments are appropriate. Pre-placement medical examinations can establish base-line data that may provide the basis for comparison in the event a laboratory-acquired illness occurs.

b. Periodic

Periodic medical examinations of laboratory workers actively engaged in large-scale research or production activities, using BSL-3 containment at laboratory scale quantities of organisms containing recombinant DNA, provide the opportunity to update the employee's work history and to ensure that the employee has the opportunity to bring to the attention of Employee Health any condition which may require more extensive examination. Updating the work and medical histories of the laboratory worker is achieved by having the worker periodically prepare and transmit to Employee Health an interval medical report. Employee Health reviews each report and determines whether medical consultation is required. If so, an appointment is then scheduled with the laboratory worker.

7. RECORDS

Health records are maintained at Employee Health. A laboratory worker may request access to their health records through Employee Health. Employee Health will assure that access is provided in a reasonable time, place and manner.

E: EDUCATION AND TRAINING REQUIREMENTS UNDER THE NIH GUIDELINES

1. Principal Investigator's Roles and Responsibilities

a. **Principal Investigator's general responsibilities:** As part of the general responsibilities under the NIH Guidelines, the Principal Investigator must:

i) Initiate or modify no recombinant DNA research which requires Institutional Biosafety Committee approval prior to initiation (see Sections III-A, III-B, III-C, III-D, and III-E, *Experiments Covered by the NIH Guidelines*) until that research or the proposed modification thereof has been approved by the Institutional Biosafety Committee and has met all other requirements of the *NIH Guidelines*

ii) Determine whether experiments are covered by Section III-E, *Experiments that Require Institutional Biosafety Committee Notice Simultaneous with Initiation*, and ensure that the appropriate procedures are followed;

iii) Report any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses to the Biological Safety Officer (where applicable), Greenhouse/Animal Facility Director (where applicable), Institutional Biosafety Committee, NIH/OBA, and other appropriate authorities (if applicable) within 30 days. Reports to NIH/OBA shall be sent to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax);

iv) Report any new information bearing on the *NIH Guidelines* to the Institutional Biosafety Committee and to NIH/OBA. Reports to NIH/OBA shall be sent to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax);

v) Be adequately trained in good microbiological techniques;

vi) Adhere to Institutional Biosafety Committee approved emergency plans for handling accidental spills and personnel contamination; and

vii) Comply with shipping requirements for recombinant DNA molecules (see Appendix H, *Shipment*, for shipping requirements and the *Saint Louis University's Guide to Shipping Biological Materials* for technical recommendations).

b) **Principal Investigator's responsibilities prior to initiating research with rDNA:**

i) Make available to all laboratory staff the protocols that describe the potential biohazards and the precautions to be taken;

ii) Instruct and train laboratory staff in: (i) the practices and techniques required to ensure safety, and (ii) the procedures for dealing with accidents; and

iii) Inform the laboratory staff of the reasons and provisions for any precautionary medical practices advised or requested (e.g., vaccinations or serum collection).

c) **Principal Investigator's responsibilities during the conduct of rDNA research:**

i) Supervise the safety performance of the laboratory staff to ensure that the required safety practices and techniques are employed;

ii) Investigate and report any significant problems pertaining to the operation and implementation of containment practices and procedures in writing to the Biological Safety Officer (where applicable), Greenhouse/Animal Facility Director (where applicable), Institutional Biosafety Committee, NIH/OBA, and other appropriate authorities (if applicable). Reports to NIH/OBA shall be sent to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax).
iii) Correct work errors and conditions that may result in the release of recombinant DNA materials; and
iv) Ensure the integrity of the physical containment (e.g., biological safety cabinets) and the biological containment (e.g., purity and genotypic and phenotypic characteristics).
v) Comply with reporting requirements for human gene transfer experiments conducted in compliance with the *NIH Guidelines* (see Appendix M-I-C, *Reporting Requirements*).

d) **Information to be submitted by the Principal Investigator to NIH OBA:**
i) Submit information to NIH/OBA for certification of new host-vector systems;
ii) Petition NIH/OBA, with notice to the Institutional Biosafety Committee, for proposed exemptions to the *NIH Guidelines*;
iii) Petition NIH/OBA, with concurrence of the Institutional Biosafety Committee, for approval to conduct experiments specified in Sections III-A-1, *Major Actions Under the NIH Guidelines*, and III-B, *Experiments that Require NIH/OBA and Institutional Biosafety Committee Approval Before Initiation*;
iv) Petition NIH/OBA for determination of containment for experiments requiring case-by-case review; and
v) Petition NIH/OBA for determination of containment for experiments not covered by the *NIH Guidelines*.
vi) Ensure that all aspects of Appendix M have been appropriately addressed prior to submission of a human gene transfer experiment to NIH OBA, and provide a letter signed by the Principal Investigator(s) on institutional letterhead acknowledging that the documentation being submitted to NIH OBA complies with the requirements set forth in Appendix M. No research participant shall be enrolled (see definition of enrollment in Section I-E-7) in a human gene transfer experiment until the RAC review process has been completed (see Appendix M-I-B, *RAC Review Requirements*); IBC approval (from the clinical trial site) has been obtained; Institutional Review Board (IRB) approval has been obtained; and all applicable regulatory authorization(s) have been obtained.
vii) For a clinical trial site that is added after the RAC review process, no research participant shall be enrolled (see definition of enrollment in Section I-E-7) at the clinical trial site until the following documentation has been submitted to NIH OBA: (1) IBC approval (from the clinical trial site); (2) IRB approval; (3) IRB-approved informed consent document; (4) curriculum vitae of the principal investigator(s) (no more than two pages in biographical sketch format); and (5) NIH grant number(s) if applicable.

e) **Submissions by the Principal Investigator to the Institutional Biosafety Committee: Submissions to do rDNA research must include:**
i) Make an initial determination of the required levels of physical and biological containment in accordance with the *NIH Guidelines*;

ii) Select appropriate microbiological practices and laboratory techniques to be used for the research;
iii) Submit the initial research protocol and any subsequent changes (e.g., changes in the source of DNA or host-vector system), if covered under Sections III-A, III-B, III-C, III-D, or III-E (*Experiments Covered by the NIH Guidelines*), to the Institutional Biosafety Committee for review and approval or disapproval; and
iv) Remain in communication with the Institutional Biosafety Committee throughout the conduct of the project.

2. Institutional Biosafety Committee's Roles and Responsibilities

a) **IBC Membership and Procedures:** The Institutional Biosafety Committee must be comprised of no fewer than five members so selected that they collectively have experience and expertise in recombinant DNA technology and the capability to assess the safety of recombinant DNA research and to identify any potential risk to public health or the environment. At least two members shall not be affiliated with the institution (apart from their membership on the Institutional Biosafety Committee) and who represent the interest of the surrounding community with respect to health and protection of the environment (e.g., officials of state or local public health or environmental protection agencies, members of other local governmental bodies, or persons active in medical, occupational health, or environmental concerns in the community). The Institutional Biosafety Committee shall include at least one individual with expertise in plant, plant pathogen, or plant pest containment principles when experiments utilizing Appendix P, *Physical and Biological Containment for Recombinant DNA Research Involving Plants*, require prior approval by the Institutional Biosafety Committee. The Institutional Biosafety Committee shall include at least one scientist with expertise in animal containment principles when experiments utilizing Appendix Q, *Physical and Biological Containment for Recombinant DNA Research Involving Animals*, require Institutional Biosafety Committee prior approval. When the institution conducts recombinant DNA research at BL3, BL4, or Large Scale (greater than 10 liters), a Biological Safety Officer is mandatory and shall be a member of the Institutional Biosafety Committee (see Section IV-B-3, *Biological Safety Officer*). When the institution participates in or sponsors recombinant DNA research involving human research participants, the institution must ensure that: (i) the Institutional Biosafety Committee has adequate expertise and training (using *ad hoc* consultants as deemed necessary); (ii) all aspects of Appendix M have been appropriately addressed by the Principal Investigator; (iii) no research participant shall be enrolled (see definition of enrollment in Section I-E-7) in a human gene transfer experiment until the RAC review process has been completed (see Appendix M-I-B, *RAC Review Requirements*); and (iv) final IBC approval is granted only after the RAC review process has been completed (see Appendix M-I-B, *RAC Review Requirements*). Institutional Biosafety Committee approval must be obtained from the institution at which recombinant DNA material will be administered to human research participants (rather than the site involved in manufacturing gene transfer products).

In order to ensure the competence necessary to review and approve recombinant DNA activities, it is recommended that the Institutional Biosafety Committee: (i) include persons with expertise in recombinant DNA technology, biological safety, and physical containment; (ii) include or have available as consultants persons knowledgeable in

institutional commitments and policies, applicable law, standards of professional conduct and practice, community attitudes, and the environment, and (iii) include at least one member representing the laboratory technical staff.

The institution shall file an annual report with NIH/OBA which includes: (i) a roster of all Institutional Biosafety Committee members clearly indicating the Chair, contact person, Biological Safety Officer (if applicable), plant expert (if applicable), animal expert (if applicable), human gene therapy expertise or *ad hoc* consultant(if applicable); and (ii) biographical sketches of all Institutional Biosafety Committee members (including community members).

No member of an Institutional Biosafety Committee may be involved (except to provide information requested by the Institutional Biosafety Committee) in the review or approval of a project in which he/she has been or expects to be engaged or has a direct financial interest.

The institution, that is ultimately responsible for the effectiveness of the Institutional Biosafety Committee, may establish procedures that the Institutional Biosafety Committee shall follow in its initial and continuing review and approval of applications, proposals, and activities.

b) **Institutional Biosafety Committee Functions. On behalf of the institution, the IBC is responsible for the following recombinant DNA research oversight:**

i) Reviewing recombinant DNA research conducted at or sponsored by the institution for compliance with the *NIH Guidelines* as specified in Section III, *Experiments Covered by the NIH Guidelines*, and approving those research projects that are found to conform with the *NIH Guidelines*. This review shall include: (i) independent assessment of the containment levels required by the *NIH Guidelines* for the proposed research; (ii) assessment of the facilities, procedures, practices, and training and expertise of personnel involved in recombinant DNA research; (iii) ensuring that all aspects of Appendix M have been appropriately addressed by the Principal Investigator; (iv) ensuring that no research participant is enrolled (see definition of enrollment in Section I-E-7) in a human gene transfer experiment until the RAC review process has been completed (see Appendix M-I-B, *RAC Review Requirements*), Institutional Biosafety Committee approval (from the clinical trial site) has been obtained, Institutional Review Board approval has been obtained, and all applicable regulatory authorizations have been obtained; (v) for human gene transfer protocols selected for public RAC review and discussion, consideration of the issues raised and recommendations made as a result of this review and consideration of the Principal Investigator's response to the RAC recommendations; (vi) ensuring that final IBC approval is granted only after the RAC review process has been completed (see Appendix M-I-B, *RAC Review Requirements*); and (vii) ensuring compliance with all surveillance, data reporting, and adverse event reporting requirements set forth in the *NIH Guidelines*.

ii) Notifying the Principal Investigator of the results of the Institutional Biosafety Committee's review and approval.

iii) Lowering containment levels for certain experiments as specified in Section III-D-2-a, *Experiments in which DNA from Risk Group 2, Risk Group 3, Risk Group 4, or*

Restricted Agents is Cloned into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems.

iv) Setting containment levels as specified in Sections III-D-4-b, *Experiments Involving Whole Animals*, and III-D-5, *Experiments Involving Whole Plants*.

v) Periodically reviewing recombinant DNA research conducted at the institution to ensure compliance with the *NIH Guidelines*.

vi) Adopting emergency plans covering accidental spills and personnel contamination resulting from recombinant DNA research.

vii) Reporting 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/OBA within 30 days, unless the Institutional Biosafety Committee determines that a report has already been filed by the Principal Investigator. Reports to NIH/OBA shall be sent to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax).

viii) The Institutional Biosafety Committee may not authorize initiation of experiments which are not explicitly covered by the *NIH Guidelines* until NIH (with the advice of the RAC when required) establishes the containment requirement.

ix) Performing such other functions as may be delegated to the Institutional Biosafety Committee under Section IV-B-2, *Institutional Biosafety Committee*.

3. Research covered by the NIH Guidelines

a) **Overview** - The NIH Guidelines classify recombinant DNA research into several categories, each requiring different levels of review and approval - and in most cases, this review and approval must occur BEFORE the work is performed. A summary of the NIH classifications of recombinant DNA experiments, and the required level(s) of approval are as follows:

i) **Experiments that Require IBC, NIH RAC Review and NIH Director Approval Before Initiation**

(1) These protocol are considered "Major Actions" and include the deliberate transfer of a drug resistance trait to a microorganism that is not known to acquire the trait naturally, if the acquisition of the drug resistant trait could affect the use of the drug to control the disease in humans, animals, or agriculture. For example, inserting a chloramphenicol-resistant trait into an infectious agent would fall under this category because chloramphenicol is still widely used in low income countries against a wide variety of microorganisms.

ii) **Experiments that Require NIH/OBA and IBC Approval Before Initiation**

(1) Protocol involving the cloning of toxin molecules with an LD50 of less than 100 ng/kg body weight fall into this category.

iii) **Experiments that Require IBC and IRC and RAC Review Before Research Participation Enrollment**

(1) Experiments involving the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into one or more research participants fall into this category. These protocol, often called human gene transfer protocol, may

include the deliberate transfer of the DNA or RNA into humans as a marker in a cell, to compensate for defective genes, to produce a potentially therapeutic substance, or to trigger the immune system to fight disease.

iv) **Experiments that Require IBC Approval Before Initiation**

(1) Several categories of protocol fall under this section including:

(a) Experiments involving the introduction of recombinant DNA into risk group 2, 3 or 4 agents (mostly BSL2, BSL3, and BSL4 organisms)

(b) Experiments in which DNA from risk group 2, 3 or 4 agents (mostly BSL2, BSL3, and BSL4 organisms) is transferred into nonpathogenic prokaryotes or lower eukaryotes

(c) Experiments involving the use of infectious DNA or RNA viruses or defective DNA or RNA viruses in the presence of helper virus in tissue culture systems

(d) Experiments involving whole animals, including the creation of transgenic organisms other than rodents and the introduction of recombinant DNA or RNA into whole animals

(e) Experiments involving whole plants

(f) Experiments involving more than 10 liters of culture

v) **Experiments that Require IBC Notice Simultaneous with Initiation**

(1) Several categories of protocol fall under this section including:

(a) Experiments involving the formation of recombinant DNA molecules containing no more than 2/3 of the genome of any eukaryotic virus

(b) Experiments involving the creation or mating of transgenic rodents

(c) Experiments that don't fall into any other category, such as experiments involving the introduction of risk group 1 DNA/RNA , any non toxin coding DNA sequence into a EK1 or EK2 host-vector system such as those derived from E. coli K-12, or non-viral risk group 1 or 2 DNA/ENA propagated in tissue culture systems.

vi) **Experiments Exempt From NIH Guidelines but Which Require Notification of the Saint Louis University IBC**

(1) Several categories of protocol fall under this section including:

(a) Experiments that are not in organisms or viruses

(b) Experiments that consist entirely of DNA from a prokaryotic host when propagated only in that host or those that consist entirely of DNA from a eukaryotic host when propagated only in that host.

(c) Experiments involving recombinant DNA containing less that ½ of any eukaryotic viral genome propagated and maintained in cells in tissue culture.