

The NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

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Thanks to the University of Kentucky
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INTRODUCTION

Recombinant DNA (rDNA) is regulated by the **National Institutes of Health (NIH)**. NAU, along with all other institutions which use rDNA in research, is required to provide training to the researchers who use rDNA. This training will provide the information you need to understand individual responsibilities and comply with the law.

To complete this training you will need to:

- Read the presentation.
- Complete the Exam. This is a 10 question exam worth 100 points. You must receive a total score of 80% to fulfill your requirement.

If you have any questions concerning the material or test results, please contact the Office of Regulatory Compliance Biological Safety Office at Shelley.Jones@nau.edu or 928-523-7268. Your questions will be answered in a timely manner. Thank you for taking the time to complete your required training.

WHAT IS THIS TRAINING?

- Recombinant DNA (rDNA) work is regulated by the **National Institutes of Health (NIH)**. All rDNA research conducted at NAU is required to comply with *NIH Guidelines*.
- NAU, along with all other institutions which use rDNA in research and receive NIH funding, is required to provide training to the researchers who use rDNA.
- This training will provide the information you need to understand individual and institutional responsibilities and comply with the law.
- It will also familiarize you with the types of rDNA experiments that require approval.

WHAT ARE THE PI'S RESPONSIBILITIES?

- All research that uses rDNA must be reported to the Institutional Biosafety Committee (IBC) and be approved.
- All researchers must understand which classification of rDNA use covers their work.
- This training will explain these responsibilities and the scope of the ***NIH Guidelines***.

RECOMBINANT DNA ADVISORY COMMITTEE (RAC) AND OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)

The NIH established the **Recombinant DNA Advisory Committee (RAC)** on October 7, 1974, in response to public concerns regarding the safety of manipulating genetic material through the use of recombinant DNA techniques.

In keeping with its role as a federal advisory committee, the RAC issues recommendations to the NIH Director that are conveyed through the **NIH Office of Biotechnology Activities (OBA)**, which is responsible for the NIH system of oversight of recombinant DNA in research.

NIH GUIDELINES

The NIH Guidelines is a publication from Department of Health & Human Services, the National Institutes of Health, and the Office of Biotechnology Activities (OBA), that outlines the minimum regulatory requirements to be followed by any entity that utilizes rDNA in research.

http://oba.od.nih.gov/oba/rac/Guidelines/NIH_Guidelines.htm

1. provides background information,
2. determines risk assessment criteria,
3. establishes a structure of oversight,
4. specifies roles and responsibilities, and
5. describes experiments that are covered by the regulations.

NAU's investigators are required to adhere to these regulations.

NIH GUIDELINES: PURPOSE

- The purpose of *NIH Guidelines* (**contained in Section I**) is to specify practices for constructing and handling:
 - rDNA molecules, and
 - organisms and viruses containing rDNA molecules.
- rDNA is defined by *NIH Guidelines* as:
 - 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
 - Molecules that result from the replication of those described above, or
 - Synthetic DNA segments which are likely to yield a potentially harmful polynucleotide or polypeptide (e.g., a toxin or a pharmacologically active agent).

MEETING NIH GUIDELINES REQUIREMENTS

- As a condition of NIH funding for rDNA research, institutions must ensure that such research conducted at or sponsored by the institution, irrespective of the source of funding, or if research is unfunded, shall comply with *NIH Guidelines*.
- NAU applies *NIH Guidelines* to all research, regardless of funding source.
- Non-compliance may result in...
 - Suspension, limitation, or termination of financial assistance for the noncompliant NIH-funded research project and of NIH funds for other rDNA research at NAU, or
 - The requirement for prior NIH approval of any and/or all rDNA projects at NAU.

At NAU, noncompliance may result in suspension, limitation, or termination of financial assistance for any noncompliant research project, regardless of funding source.

ADDITIONALLY, NIH GUIDELINES CONTAIN . . .

- **Guidance for safety considerations (Section III)**
 - Risk Assessment
 - Risk Groups
 - Containment
- **A listing of experiments that are covered by the NIH Guidelines (Section III).**
- **REMEMBER:** Your research falls within Section III.

RISK ASSESSMENT AND PRACTICES: SECTION 11-A,B

- Initial risk assessment is made by the investigator based on Risk Group (RG).
- **Risk Group Classification:** Agents are classified relative to pathogenicity for healthy adults. The level of Risk Group is assigned a containment level as well (BSL1 through BSL3 at NAU).
- Standard practices are described as well as special procedures, equipment, laboratory installations for physical barriers, and biological barriers, such as vectors with limited infectivity for specific hosts or diminished capacity for dissemination and survival in the environment.

CONTAINMENT: SECTION 11-B (CONTINUED)

The appendices of NIH Guidelines provide information for specific situations. For instance:

- [Appendix G](#) specifies physical containment for standard laboratory experiments, including animals housed in a vivarium.
- [Appendix I](#) specifies biological barriers that may be used.
- [Appendix P](#) describes plant-specific biosafety levels (BSL1-P through BSL4-P) and specifies appropriate containment and practices.
- [Appendix Q](#) describes large animal-specific biosafety levels (BSL1-N through BSL4-N) and specifies containment and practices.

STRUCTURE OF OVERSIGHT NAU POLICIES FOR USE OF RDNA

All institutions that conduct scientific research involving rDNA and receive federal funding are required to have an Institutional Biosafety Committee (IBC). The use of rDNA is considered “biological research.”

The IBC requires that researchers complete a disclosure form which provides information about the proposed biological research.

IBC policies at NAU regarding biological research are set according to guidelines provided by the NIH and the Centers for Disease Control and Prevention (CDC).

THE IBC AT NAU

NAU's IBC meets periodically as needed and at least annually to review proposals. All biological research performed at NAU must be described on a disclosure form that is submitted to the IBC.

Committee members review the submitted disclosure prior to the meeting where it will be presented.

The Principal Investigator (PI) listed on the disclosure, or a representative, may be invited to attend the meeting to help the committee understand the proposed research.

Work may not commence until approved by the IBC.

THE IBC AT NAU

As you complete your disclosure, you will see a form that lists classification of rDNA work; these categories are described in Section III of the *NIH Guidelines*, <http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines>.

Your IBC disclosure provides a brief summary of the classifications, so that you can determine which one covers the research you do with rDNA. When completing your disclosure, you are asked to check each box that applies to your rDNA research.

According to the *NIH Guidelines*, determination and understanding of which classification covers rDNA research is determined by the PI.

IBC members will assist you if your rDNA research is difficult to place into one of these classifications. Also, NAU's Office of Regulatory Compliance is here to assist you with any questions or concerns at 928-523-7268.

NIH GUIDELINES ROLES & RESPONSIBILITIES (SECTION IV)

The NIH Guidelines assign responsibilities to different entities:

- Institution
 - **Section IV-B**
- Institutional Biosafety Committee
 - **Section IV-B-2**
- Biosafety Officer
 - **Section IV-B-3**
- Principal Investigator
 - **Section IV-B-7**

INSTITUTIONAL RESPONSIBILITIES

Section IV-B-1 General Information The Institution (NAU) shall:

- **Section IV-B-1-a** Establish and implement policies that provide for the safe conduct of recombinant DNA research and that ensure compliance with the *NIH Guidelines*.
- **Section IV-B-1-b** Establish an IBC with appropriate expertise and training;
- **Section IV-B-1-c** Appoint a Biosafety Officer for the institution;
- **Section IV-B-1-h** Ensure appropriate training;
- **Section IV-B-1-i** Determine the necessity for health surveillance of personnel;
- **Section IV-B-1-j** Report any significant problems, violations, or research-related accidents/illnesses to OBA.

INSTITUTIONAL RESPONSIBILITIES

The NIH mandates that IBCs will...

- Ensure rDNA research does not endanger the safety of:
 - Researchers
 - Technicians
 - Research Subjects
 - Community
 - Environment

THE INSTITUTIONAL BIOSAFETY COMMITTEE OVERVIEW

- *NIH Guidelines* requires that research involving rDNA is registered with the IBC. All rDNA research conducted at NAU must be registered with the IBC, even that which is exempt from the *NIH Guidelines*.
- The *NIH Guidelines* also stipulate that additional procedures, depending on IBC risk assessment, may be established as deemed necessary by the institution.
- NAU adheres to the *Guidelines* by requiring registration of rDNA, infectious agents (including bacteria, virus, fungi, parasites or other microorganisms), materials of human origin, and Select Agents and Toxins.

BIOSAFETY OFFICER RESPONSIBILITIES

The position of Biosafety Officer (BSO) is mandated by NIH if the institution conducts:

- rDNA research at BSL3 or 4, or
- Large-scale research (>10L of culture).

Biosafety Officer responsibilities:

- Serves as administrator for reporting to the IBC;
- Advises IBC on biosafety and regulatory issues;
- Conducts periodic lab inspections for the IBC.

NAU's Biosafety Officer is Shelley Jones, 928-523-7268.

PRINCIPAL INVESTIGATOR (PI) RESPONSIBILITIES

Section IV-B-7 The Principal Investigator shall:

- Determine which experiments are covered by NIH Guidelines
- Understand the classification within Section III that covers the rDNA research.
- Comply with NIH Guidelines.
- Register with IBC prior to initiation of experiments.
- Report changes in research protocols immediately.
- Annually verify protocol details.
- Adhere to IBC-approved emergency plans.
- Assess integrity of containment.
- Train and supervise lab staff appropriately.
- Report to the Biosafety Officer and IBC any incidents involving rDNA, contact Shelley Jones at 928-523-7268).

PRINCIPAL INVESTIGATOR (PI) RESPONSIBILITIES (CONTINUED)

PIs are responsible for...

- Instructing and training laboratory staff in:
 - Practices and techniques required to maintain safety, and
 - Procedures for dealing with lab accidents;
- Informing laboratory staff of any precautionary medical practices;
- Supervising safety performance of lab staff.
- Reporting any significant problems, violations of the NIH Guidelines, or any significant research-related accidents and illnesses to the Biological Safety Officer/IBC, within 30 days.
- Failure to do so may jeopardize your funding and the continuation of your research!

And remember, to comply with the Guidelines, it is important that you understand the classification within Section III that covers your research involving rDNA.

EXPERIMENTS COVERED BY NIH GUIDELINES

All experiments with recombinant DNA fall into one of the Section III classifications. NIH requires that researchers understand which classification covers their work. The following slides describe each of the Section III classifications, including those that are not shown on the IBC disclosure form.

Experiments in Sections III-A, B, and C are not currently performed at NAU.

- Section III-A. These experiments require IBC approval, Recombinant DNA Advisory Committee (RAC) review, and NIH Director approval before initiation.
Example: deliberate transfer of a drug resistance trait to microorganisms not known to acquire the trait naturally, if acquisition could compromise use of the drug to control disease agents in humans, veterinary medicine, or agriculture.
- Section III-B. These experiments require NIH/OBA and IBC approval before initiation:
Example: experiments involving the cloning of toxin molecules with an LD₅₀ of less than 100 nanograms per kilogram of body weight.

EXPERIMENTS COVERED BY NIH GUIDELINES

- Section III-C. These experiments require IBC approval, Institutional Review Board (IRB) approval, and RAC review before initiation:
Example: deliberate transfer of rDNA, or DNA/RNA derived from rDNA, into one or more human research participants.
- Section III-D, E, F. These experiments require IBC approval before initiation. This includes most of NAU's research.
- There are a number of rDNA experiments which are exempt from NIH Guidelines (Section III-F), they do not pose a significant risk to health or to the environment.
- However, registration with the IBC is required at NAU for all rDNA research, regardless of whether or not it is exempt from the NIH Guidelines.

EXAMPLES OF RECOMBINANT DNA EXPERIMENTS

Most BSL1 cloning experiments will fall into one of the following categories:

- Escherichia coli K-12 Host-Vector systems, or derivatives of E. coli K-12. Appendix C-II.
- Experiments that consist entirely of DNA from a prokaryotic host including its indigenous plasmids or viruses when propagated only in that host (or a closely related strain of the same species), or when transferred to another host by well established physiological means. **Section III-F-3.** For example, a recombinant *E. coli* gene cloned into a plasmid expressed in *E. coli*.
- Experiments that consist entirely of DNA from an eukaryotic host including its chloroplasts, mitochondria, or plasmids (but excluding viruses) when propagated only in that host (or a closely related strain of the same species). **Section III-F-4.**

EXAMPLES OF RECOMBINANT DNA EXPERIMENTS

Most vaccine experiments will fall into one of the following categories:

- Experiments using Risk Group 2 or Risk Group 3 agents as Host-Vector systems. **Section III-D-1.**
 - Risk Group 2
 - Risk Group 3
- Experiments in which DNA from Risk Group 2 or Risk Group 3 agents is cloned into nonpathogenic prokaryotic or lower eukaryotic Host-Vector systems. **Section III-D-2.**
 - Risk Group 2
 - Risk Group 3

Many vaccine projects, as well as other studies involving animals, will also be covered in Section III-D-4:

- Experiments involving whole animal work.

EXAMPLES OF RECOMBINANT DNA EXPERIMENTS (CONTINUED)

Most *in vitro* infectious virus work will be covered by Section III-D-3: Experiments involving the use of infectious DNA or RNA viruses, or defective DNA or RNA viruses in the presence of a helper virus in tissue culture systems.

Work with defective viruses in the absence of helper viruses is covered by Section III-E-1: Experiments involving the formation of rDNA molecules containing no more than two-thirds of the genome of any eukaryotic virus, may be propagated and maintained in tissue culture cells at BLS1, providing that the cells have been demonstrated to lack helper virus.

Plant work in most cases is covered by *either* Section III-D-5, for BL2-P: Experiments to genetically engineer plants by rDNA methods, to use such plants for other experimental purposes (e.g., response to stress), to propagate such plants, or to use plants together with microorganisms or insects containing rDNA.

EXAMPLES OF RECOMBINANT DNA EXPERIMENTS (CONTINUED)

Or, for plants at BL1-P, by Section III-E-2:

Experiments involving rDNA-modified whole plants, and/or experiments involving rDNA-modified organisms associated with whole plants.

Use of more than 10 liters of culture containing recombinant organisms is covered by:

Section III-D-6.

Experiments involving the use of transgenic rodents, if BSL1 only, are covered by:

Section III-E-3.

RECOMBINANT DNA EXPERIMENT CLASSIFICATIONS (FULL CHECKLIST FROM IBC PROTOCOL)

This form is required to be completed for all recombinant DNA (rDNA) research. To the best of your ability, please select the classification for each type of rDNA research performed in your laboratory for this disclosure. We recommend using the NIH Guidelines rDNA Training developed by ORC or the NIH Guidelines for Research Involving Recombinant DNA http://oba.od.nih.gov/oba/rac/Guidelines/NIH_Guidelines.pdf. For assistance with this form, please contact the Biosafety Officer at 928-523-7268 or shelley.jones@nau.edu.

- Section III-F-1:** Experiments that are not in organisms or viruses.
- Section III-F-2:** Experiments that consist entirely of DNA segments from a single nonchromosomal or viral DNA source, although one or more of the segments may be a synthetic equivalent.
- Section III-F-3:** Experiments that consist entirely of DNA from a prokaryotic host including its indigenous plasmids or viruses when propagated only in that host (or a closely related strain of the same species), or when transferred to another host by well established physiological means.
- Section III-F-4:** Experiments that consist entirely of DNA from an eukaryotic host including its chloroplasts, mitochondria, or plasmids (but excluding viruses) when propagated only in that host (or a closely related strain of the same species).

RECOMBINANT DNA EXPERIMENT CLASSIFICATIONS (CONTINUED)

- Section III-F-5:** Those that consist entirely of DNA segments from different species that exchange DNA by known physiological processes, though one or more of the segments may be a synthetic equivalent. A list of such exchangers is prepared and periodically revised by the NIH Director and can be found at http://oba.od.nih.gov/oba/rac/Guidelines/NIH_Guidelines.pdf

- Section III-F-6:** Those exemptions as determined by the NIH Director to not present a significant risk to health or the environment are listed in the appendices below. Please check all categories that apply:
 - Appendix C-I:** Recombinant DNA in Tissue Culture; Molecules Containing <1/2 of any Eukaryotic Viral Genome.
 - Appendix C-II:** *Escherichia coli* K-12 Host-Vector Systems.
 - Appendix C-III:** *Saccharomyces* Host-Vector Systems.
 - Appendix C-IV:** *Bacillus Subtillus* or *Bacillus Lichenformis* Host-Vector Systems.
 - Appendix C-V:** Extrachromosomal Elements of Gram Positive Organisms.
 - Appendix C-VI:** The Purchase or Transfer of Transgenic Rodents, BSL 1 only.
 - Appendix C-VII:** Transgenic Rodents Generated by Breeding, BSL 1 only.

- Section III-E:** Experiments that are not included in Sections III-A, III-B, III-C, III-D, and III-F; and experiments in which all components are derived from non-pathogenic prokaryotes and non-pathogenic eukaryotes fall under Section III-E and may be conducted at **BSL-1 containment**.

RECOMBINANT DNA EXPERIMENT CLASSIFICATIONS (CONTINUED)

- Section III-D-3:** 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. Please select the Risk Group below:
 - Risk Group 2 (RG2):** Agents are associated with human disease which is rarely serious and for which preventative or therapeutic interventions are often available.
 - Risk Group 3 (RG3):** Agents are associated with serious or lethal human disease for which preventative or therapeutic interventions may be available.

- Section III-D-4:** Experiments involving whole animals that cannot be done at BSL 1.

- Section III-D-5:** Experiments involving whole plants or insects; experiments to genetically engineer plants by recombinant DNA methods, to use such plants for experimental purposes (e.g. response to stress), to propagate such plants, or to use plants together with microorganisms or insects containing recombinant DNA (cannot be done at BSL 1).

- Section III-D-6:** Experiments involving more than 10 liters of culture.

RECOMBINANT DNA EXPERIMENT CLASSIFICATIONS (CONTINUED)

Please note: This section requires NIH pre-approval. Please contact the IBC for assistance.

- ❑ **Section III-A-1:** The deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally. (Requires RAC review and NIH Director pre-approval)
- ❑ **Section III-B-1:** Experiments involving the cloning of toxin molecules with LD50 of less than 100 nanograms per kilogram body weight. (Requires NIH pre-approval)
- ❑ **Section III-C-1:** Experiments involving the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into one or more human research participants. (Requires NIH pre-approval)

DUAL USE RESEARCH OF CONCERN (DURC)

- Despite its value and benefits, certain types of research conducted for legitimate purposes can be utilized for both benevolent and harmful purposes. Such research is called “dual use research of concern (DURC).”
- The United States Government’s oversight of DURC is aimed at preserving the benefits of life science research while minimizing the risk of misuse of the knowledge, information, products, or technologies provided by such research.
- In addition to IBC review, research of this type must also be reviewed by the Institutional Review Entity (IRE).
- If you are unsure if your research is subject to IRE review, please contact NAU’s biosafety officer, Shelley Jones at 928-523-7268.

EXAMPLES OF DURC

An experiment May be considered DURC if it:

- Enhances the harmful consequences of the agent or toxin.
- Disrupts immunity or effectiveness of an immunization against the agent or toxin, without clinical and/or agricultural justification.
- Confers to the agent or toxin resistance to clinically and/or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates their ability to evade detection methodologies.
- Increases the stability, transmissibility or the ability to disseminate the agent or toxin.
- Alters the host range or tropism of the agent or toxin.
- Enhances the susceptibility of a host population to the agent or toxin.
- Generates or reconstitutes an eradicated or extinct agent or toxin listed in the definition of DURC Agents.
- For more information, please visit <http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/dual-use-research-concern>.

NEED MORE INFORMATION?

For more information on the topics covered in this training, check these websites:

Biosafety in Microbiological and Biomedical Laboratories

<http://www.cdc.gov/biosafety/publications/bmbl5/index.htm>

NIH Guidelines and DURC

<http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines>

<http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/dual-use-research-concern>

NAU

<http://www.research.nau.edu/compliance/orc/biosafety.aspx>

QUESTIONS?

Please email Shelley.Jones@nau.edu with any specific questions or concerns.

Thank you and good luck with your research!