2016

Recombinant DNA Procedural Manual

Environmental Health & Safety

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EHS Biological Safety Staff
University of Iowa

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I Summary

All non-exempt research[1] involving recombinant or synthetic nucleic acid molecules must comply with the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*). The *NIH Guidelines*, which are published in the Federal Register, define allowable practices for the construction and handling of recombinant or synthetic nucleic acid molecules and their introduction into viruses and cells. Under the *NIH Guidelines*, the Institutional Biosafety Committee (IBC) is charged with assessing the risk of and determining the biosafety containment level required for all proposed recombinant or synthetic nucleic acid research.

Investigators intending to perform any non-exempt research involving recombinant or synthetic nucleic acids must describe such proposed research in a recombinant or synthetic nucleic acid Registration Document and submit it to the IBC for review. Research involving non-exempt recombinant or synthetic nucleic acids cannot be initiated without prior, specific IBC approval. Such approval is required regardless of the source of funding of the proposed research.

[1]Exempt recombinant or synthetic nucleic acid research is defined under Section III-F in the *NIH Guidelines*.

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II Scope

The *NIH Guidelines* and the procedures summarized in this document apply to all non-exempt recombinant and synthetic nucleic acids research performed at the University of Iowa.

III Reference Regulations

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (*NIH Guidelines*), April 2016[1] and subsequent revisions.

[1]*Guidelines*. http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines

IV Definitions

APHIS: Animal and Plant Health Inspection Service

BSO: Biological Safety Officer

DSP: Division of Sponsored Programs

DURC: Dual Use Research of Concern: life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential negative consequences to public health and safety, agricultural crops and other plants, animals, the environment, material, or national security in the foreseeable future[1]

EHS: Environmental Health & Safety

IBC: Institutional Biosafety Committee

IO: Institutional Official

NIH: National Institutes of Health

NIH OSP: Office of Science Policy, Office of the Director, NIH

NSABB: National Science Advisory Board for Biosecurity

PI: Principal Investigator

RAC: Recombinant DNA Advisory Committee, Office of the Director, NIH

rDNA (recombinant deoxyribonucleic acid): 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.

rsNAM (recombinant or synthetic nucleic acid molecules): defined as: (i) molecules that a) are constructed by joining nucleic acid molecules and b) can replicate in a living cell, i.e., recombinant nucleic acids; (ii) nucleic acid molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, i.e., synthetic nucleic acids; or (iii) molecules that result from the replication of those described in (i) or (ii) above.

rDNARD: rDNA Registration Document

Synthetic DNA: Synthetic DNA segments which are likely to yield a potentially harmful polynucleotide or polypeptide are considered as equivalent to their natural DNA counterpart.

USDA: United States Department of Agriculture

Asst VPR: Assistant Vice President for Research Compliance

[1]United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern

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V Responsibilities

a. University responsibilities

The University is responsible for ensuring that rsNAM activities comply with the *NIH Guidelines*. Compliance authority on campus is placed with the IBC, appointed by and advisory to the Vice President for Research. According to its charge, this committee:

- Ensures compliance with the *NIH Guidelines* for all non-exempt rsNAM research conducted at or sponsored by the University through:
    - An independent assessment of the containment levels required by the *NIH Guidelines* for the proposed research.
    - An assessment of the facilities, procedures, practices, and training and expertise of personnel involved in rsNAM research.
    - Ensuring that all aspects of Appendix M have been appropriately addressed by a PI involved in human gene transfer experiments.
    - Consideration of the criteria for selecting protocols for Recombinant DNA Advisory Committee (RAC).
    - Ensuring final IBC approval is granted only after the NIH protocol registration process has been completed.
    - Ensuring compliance with all surveillance, data reporting, and adverse event reporting as required by the *NIH Guidelines*.
    - Review periodically rsNAM research being conducted at the University to ensure compliance with the *NIH Guidelines*.
    - Reporting within 30 days to the Institutional Official and to the NIH any significant problems with or violations of the *NIH Guidelines* and any significant research-related accidents or illnesses. Spills or accidents in BSL2 labs resulting in an overt exposure must be immediately reported to NIH OSP; spills or accidents occurring in BSL3 labs resulting in an overt or potential exposure must be immediately reported to NIH OSP.
    - Prohibiting the initiation of experiments not explicitly covered by the *NIH Guidelines* until NIH establishes the required containment.
    - Performing other functions as may be delegated to the committee by the *NIH Guidelines*.
- Provides consultation to Environmental Health & Safety (EHS) and PIs handling biohazards, including reviewing emergency plans covering accidental spills and personnel contamination resulting from such research.
- Requires that each member complete the training course “rDNA research, *NIH Guidelines*,” available online through the EHS website. In addition, information will periodically be discussed during IBC meetings that will provide updates to members’ training.

b. EHS biosafety office responsibilities

The EHS Biosafety Office will:

- Initiate electronic notices of approval to PIs for rsNAM projects approved by the IBC.
- Maintain a database of approved rsNAM projects to assist in an annual review process (see below), informing PIs of upcoming expirations of IBC approvals and request resubmission or cancelation.
- Advise PIs in matters of biosafety including precautions to take when handling biohazardous materials.
- Perform audits and inspections of laboratories in which approved rsNAM projects are being performed.
- Develop emergency plans for handling accidental spills and personnel contamination and investigate laboratory accidents involving rsNAM research.
- Provide advice on laboratory security.

c. Principal investigator responsibilities

Principal Investigators conducting rsNAM research are responsible for full compliance of the *NIH Guidelines*. These responsibilities are outlined in Section IV-B-7 of the *NIH Guidelines*.

i General requirements

- Initiate or modify rsNAM research subject to the *NIH Guidelines* only after that research or the proposed modification thereof, has been approved by the IBC and has met all other requirements of the *NIH Guidelines*.
- Determine the classification of the experiment and follow appropriate registration procedures.
- Report within 30 days to the Biosafety Officer (BSO), IBC and NIH OSP all significant problems with and violations of the *NIH Guidelines* and all significant research-related accidents and illnesses. Spills or accidents in BSL2 labs resulting in an overt exposure and any spills or accidents occurring in BSL3 labs must be immediately reported to the BSO, IBC and NIH OSP.
- Report new information bearing on the *NIH Guidelines* to the IBC and NIH OSP.
- Be adequately trained in good microbiological techniques.
- Adhere to IBC approved emergency plans for dealing with accidental spills and personnel contamination.
- Comply with shipping requirements for rsNAM molecules (Appendix H of the *NIH Guidelines*).

ii In submissions to the NIH OSP

- Submit information to NIH OSP for certification of new host-vector systems.
- Petition NIH OSP, with notice to the IBC, for proposed exemptions to the *NIH Guidelines*.

- Petition NIH OSP, with concurrence to the IBC, for approval to conduct experiments specified in Sections III-A-1 and III-B.
- Petition NIH OSP for determination of containment for experiments requiring case-by-case review or for experiments not covered by the *NIH Guidelines*.
- Ensure that all aspects of Appendix M have been appropriately addressed.

iii In submissions to the IBC

- Make an initial determination of the required levels of physical and biological containment in accordance with the *NIH Guidelines*.
- Submit the initial research protocol and any subsequent changes to the IBC for review and approval or disapproval.
- Remain in communication with the IBC throughout the conduct of the project.

iv Prior to and during the conduct of the research

- Make available to all lab staff the protocols that describe the potential biohazards, the precautions to be taken, and procedures for dealing with accidents.
- Train and supervise laboratory staff to ensure that the required safety practices and techniques are employed.
- Inform the lab staff of the reasons and provisions for any precautionary medical practices advised or requested (e.g., vaccinations or serum collection).
- Investigate and report any significant problems pertaining to the operation and implementation of containment practices and procedures to the Biological Safety Officer (BSO), IBC, NIH OSP, and other appropriate authorities, if applicable.
- Ensure the integrity of the physical containment (biological safety cabinets) and the biological containment (purity, genotypic and phenotypic characteristics) and correct work errors and conditions that may result in release of rsNAM materials.
- Comply with reporting requirements for human gene transfer experiments (see Appendix M-I-C).

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VI Containment Guidelines for Experiments Covered by the *NIH Guidelines*

Experiments involving recombinant or synthetic nucleic acid molecules are divided into six classes.

a. Class III-A experiments

Class III-A experiments require IBC and Recombinant DNA Advisory Committee (RAC) review and NIH Director Approval before initiation. These experiments include the deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally, if such

acquisition could compromise the use of the drug to control disease agents in human or veterinary medicine or agriculture.

b. Class III-B experiments

Class III-B experiments require NIH OSP and IBC approval before initiation. These experiments include the deliberate formation of rsNAM containing genes for the biosynthesis of toxin molecules lethal for vertebrates at an LD50 of less than 100 nanograms per kilogram body weight. Specific approval has been given for the cloning in *Escherichia coli* K-12 of DNA containing genes coding for the biosynthesis of toxic molecules which are lethal to vertebrates at 100 nanograms to 100 micrograms per kilogram body weight. Experiments in this category cannot be initiated without submission of relevant information on the proposed experiment to NIH OSP. The containment conditions for such experiments will be determined by NIH OSP in consultation with ad hoc experts.

c. Class III-C experiments

Class III-C experiments require IBC and Institutional Review Board (IRB) approvals and NIH protocol registration before research participant enrollment. These experiments involve the deliberate transfer of recombinant or synthetic nucleic acids, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into one or more human research participants. Human gene transfer is the deliberate transfer into human research participants of either:

- Recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules, or
- Synthetic nucleic acid molecules, or DNA or RNA derived from synthetic nucleic acid molecules, that meet any one of the following criteria:
  - Contain more than 100 nucleotides; or
  - Possess biological properties that enable integration into the genome (e.g., cis elements involved in integration); or
  - Have the potential to replicate in a cell; or
  - Can be translated or transcribed.

PIs shall submit relevant information on the proposed human gene transfer experiments for IBC and IRB review and discussion and subsequently to the NIH OSP; see Appendix M-I-A of the *NIH Guidelines*, Requirements for Protocol Submission. The information provided in response to Appendix M should not contain any confidential commercial information or trade secrets, enabling all aspects of RAC review to be open to the public, if applicable. If a human gene transfer experiment requires public RAC review, NIH OSP will send a letter within 10 working days after completion of the RAC meeting to the PI, summarizing RAC comments and recommendations (if any).

For a clinical trial site that is added after the NIH protocol registration process, the PI must submit the following documentation to NIH OSP within 30-days of research participant

enrollment: IBC approval (from the clinical trial site), IRB approval, IRB-approved informed consent document, and NIH grant number(s), if applicable.

d. Class III-D experiments

Class III-D experiments require IBC approval and submission of an rDNA Registration Document prior to initiation. These experiments are divided into seven categories.

i The use of risk group 2, risk group 3, risk group 4, or restricted agents as host-vector systems

Experiments involving the introduction of rsNAM into risk group 2 agents will usually be conducted at Biosafety Level (BSL) 2 containment. Experiments with such agents will usually be conducted with whole animals at BSL2 or Animal BSL (ABSL) 2 containment. Experiments involving the introduction of rsNAM into risk group 3 agents will usually be conducted at BSL3 containment. Experiments with such agents will usually be conducted with whole animals at BSL3 or ABSL3 containment. Experiments involving the introduction of rsNAM into risk group 4 agents shall be conducted at BSL4 containment. Experiments with such agents will usually be conducted with whole animals at BSL4 or ABSL4 containment; however, no BSL4 facility is available for such work at the University of Iowa. Containment conditions for experiments involving the introduction of rsNAM into restricted agents shall be set on a case-by-case basis following NIH OSP review. A USDA/APHIS permit is required for work with plant or animal pathogens. Experiments with such agents shall be conducted with whole animals at BSL4 or ABSL4 containment; however, as noted above, no BSL4 facility is available for working with animals requiring ABSL4 containment.

ii Cloning DNA from risk group 2, risk group 3, risk group 4, or restricted agents into nonpathogenic prokaryotic or lower eukaryotic host-vector systems

Experiments in which DNA from Risk Group 2 or 3 agents is transferred into nonpathogenic prokaryotes or lower eukaryotes may be performed under BSL2 containment. Experiments in which DNA from Risk Group 4 agents is transferred into nonpathogenic prokaryotes or lower eukaryotes may be performed under BSL2 containment after demonstration that only a totally and irreversibly defective fraction of the agent's genome is present in a given recombinant. In the absence of such a demonstration, BSL4 containment shall be used. The IBC may approve the specific lowering of containment for particular experiments to BSL1. Many experiments in this category are exempt from the *NIH Guidelines* (see Section III-F). Experiments involving the formation of rsNAM for certain genes coding for molecules toxic for vertebrates require NIH OSP approval (see Class III-B experiments) or shall be conducted under NIH specified conditions as described in Appendix F of the *NIH Guidelines*. Containment conditions for experiments in which DNA for restricted agents is transferred into

nonpathogenic prokaryotes or lower eukaryotes shall be determined by NIH OSP following a case-by-case review. A USDA permit is required for work with plant or animal pathogens.

iii The use of infectious DNA or RNA viruses or defective DNA or RNA viruses in the presence of helper virus in tissue culture systems

Experiments involving the use of infectious or defective Risk Group 2 viruses in the presence of helper virus may be conducted at BSL2. Experiments involving the use of infectious or defective Risk Group 3 viruses in the presence of helper virus may be conducted at BSL3. Experiments involving the use of infectious or defective Risk Group 4 viruses in the presence of helper virus may be conducted at BSL4. Experiments involving the use of infectious or defective restricted poxviruses in the presence of helper virus shall be determined on a case-by-case basis following NIH OSP review. Experiments involving the use of infectious or defective viruses in the presence of helper virus which are not covered in the experiments just described may be conducted at BSL1.

iv Whole animals

Experiments involving whole animals in which the animal's genome has been altered by stable introduction of rsNAM, or nucleic acids derived therefrom, into the germ-line (transgenic animals) and experiments involving viable recombinant or synthetic nucleic acid molecule-modified microorganisms tested on whole animals fall under this section. rsNAM, or DNA or RNA molecules derived therefrom, from any source except for greater than two-thirds of eukaryotic viral genome, may be transferred to any non-human vertebrate or any invertebrate organism and propagated under conditions of physical containment comparable to BSL1 or ABSL1 and appropriate to the organism under study. Animals that contain sequences from viral vectors, which do not lead to transmissible infection either directly or indirectly as a result of complementation or recombination in animals, may be propagated under conditions of physical containment comparable to BSL1 or ABSL1 and appropriate to the organism under study. Exceptions under this section involve the generation of transgenic rodents that require BSL1 containment (described under Section III-E) and the purchase or transfer of transgenic rodents; the latter of which is exempt from the *NIH Guidelines* under Section III-F.
A USDA permit is required for work with plant or animal pathogens.

v Whole plants

Plant BSL (BSL-P) 3 or BSL2-P+ biological containment is recommended for experiments involving most exotic infectious agents with recognized potential for serious detrimental impact on managed or natural ecosystems when rsNAM techniques are associated with whole plants. BSL3-P or BSL2-P+ biological containment is recommended for experiments involving plants containing cloned genomes of readily transmissible exotic infectious agents with recognized potential for serious detrimental effects on managed

or natural ecosystems in which there exists the possibility of reconstituting the complete and functional genome of the infectious agent by genomic complementation in planta. BSL4-P containment is recommended for experiments with a small number of readily transmissible exotic infectious agents, such as the soybean rust fungus (*Phakospora pachyrhizi*) and maize streak or other viruses in the presence of their specific arthropod vectors that have the potential of being serious pathogens of major U.S. crops. BSL3-P containment is recommended for experiments involving sequences encoding potent vertebrate toxins introduced into plants or associated organisms. rsNAM containing genes for the biosynthesis of toxin molecules lethal for vertebrates at an LD50 of <100 nanograms per kilogram body weight fall under Section III-B and require NIH OSP and IBC approval before initiation. BSL3-P or BSL2-P+ biological containment is recommended for experiments with microbial pathogens of insects or small animals associated with plants if the rsNAM modified-organism has a recognized potential for serious detrimental impact on managed or natural ecosystems.

vi More than 10 liters of culture

The appropriate containment will be decided by the IBC. Where appropriate, Appendix K - Physical Containment for Large Scale Uses of Organisms Containing Recombinant or Synthetic Nucleic Acid Molecules, shall be used.

vii Experiments involving influenza viruses

Experiments with influenza viruses containing the H2 hemagglutinin (HA) segment shall be conducted at BSL3 enhanced. Experiments with the H2 HA gene in cold-adapted, live attenuated vaccine strains may be conducted at BSL2 containment provided segments with mutations conferring temperature sensitivity and attenuation are not altered in the recombinant or synthetic virus. Experiments with risk Group 2 influenza viruses containing genes from human H5N1 other than the HA gene can be worked on at BSL2. Experiments involving influenza viruses containing a majority of genes and/or segments from a HPAI H5N1 influenza virus shall be conducted at BSL3 enhanced containment. Experiments involving influenza viruses containing a minority of genes and/or segments from a HPAI H5N1 influenza virus shall be conducted at BSL3 enhanced unless a risk assessment performed by the IBC determines that they can be conducted safely at BSL2 and after they have been excluded pursuant to 9 CFR 121.3(e). Experiments involving influenza viruses containing any gene or segment from 1918 H1N1 shall be conducted at BSL3 enhanced containment. The availability of antiviral drugs as preventive and therapeutic measures is an important safeguard for experiments with 1918 H1N1, HPAI, H5N1, and human H2N2 (1957-1968). If an influenza virus containing genes from one of these viruses is resistant to both classes of current antiviral agents, adamantanes and neuraminidase inhibitors, higher containment may be required based on the risk assessment considering transmissibility to humans, virulence, pandemic potential, alternative antiviral agents if available, etc.

e. Class III-E experiments

Class III-E experiments require IBC notification and submission of an rDNA Registration Document simultaneously with initiation. Those experiments not included under Classes A, B, C, D or F are considered in this class. For example, experiments in which all components are derived from non-pathogenic prokaryotes and non-pathogenic lower eukaryotes are included in this class and can be carried out at BSL1 containment. Creation of transgenic and knockout animals, or other projects which involve modification of the genome, that may be housed at ABSL1 containment, are also classified under III-E. Additional rsNAM experiments include:

- Experiments involving the formation of rsNAM containing no more than two-thirds of the genome of any eukaryotic virus (all viruses from a single Family being considered identical). These experiments may be propagated and maintained in cells in tissue culture using BSL1 containment. For such experiments, it must be demonstrated that the cells lack helper virus for the specific Families of defective viruses being used. If helper virus is present, procedures specified under Section III-D-3 should be used. The DNA may contain fragments of the genome of viruses from more than one Family but each fragment shall be less than two-thirds of a genome, and
- Experiments involving nucleic acid molecule-modified whole plants, and/or nucleic acid molecule-modified organisms associated with whole plants, except those that fall under Section III-A, III-B, III-D, or III-F. It should be emphasized that knowledge of the organisms and judgment based on accepted scientific practices should be used in all cases in selecting the appropriate level of containment. By contrast, a lower level of containment may be appropriate for small animals associated with many types of rsNAM-modified plants.

i Experiments involving whole plants

BSL1-P is recommended for all experiments with rsNAM-containing plants and plant-associated microorganisms not covered in Section III-E-2-b or other sections of the *NIH Guidelines*. BSL2-P or BSL1-P+ biological containment is recommended for the following experiments:

- Plants modified by rsNAM that are noxious weeds or can interbreed with noxious weeds in the immediate geographic area.
- Plants in which the introduced DNA represents the complete genome of a non-exotic infectious agent.
- Plants associated with rsNAM-modified non-exotic microorganisms that have a recognized potential for serious detrimental impact on managed or natural ecosystems.
- Plants associated with rsNAM-modified exotic microorganisms that have no recognized potential for serious detrimental impact on managed or natural ecosystems.
- Experiments with rsNAM-modified arthropods or small animals associated with plants or with arthropods or small animals with rsNAM-modified

microorganisms associated with them if the rsNAM-modified microorganisms have no recognized potential for serious detrimental impact on managed or natural ecosystems.

ii Experiments involving transgenic rodents

Experiments involving the generation of rodents in which the animal's genome has been altered by stable introduction of rsNAM, or DNA derived therefrom, into the germ-line (transgenic rodents). Only experiments that require BSL1 containment are covered under this section; experiments that require BSL2, BSL3, or BSL4 containment are covered under Section III-D. Breeding transgenic/knockout rodents that may be housed under ABSL1 containment conditions are exempt under Section III-F, with the exception of:

- Breeding experiments involving transgenic rodents that contain more than 50 percent of the genome of an exogenous eukaryotic virus from a single family, in order to prevent inadvertent reconstitution of an exogenous virus in the resultant transgenic rodent; and
- Breeding experiments in which the transgenic rodent's transgene is under the control of a gammaretroviral long terminal repeat (LTR), in order to address the small risk of recombination with endogenous retroviruses which could potentially result in mobilization of the transgene via a replication-competent mouse retrovirus.

f. Class III-F experiments

Class III-F experiments are exempt from the *NIH Guidelines*; however, registration with the IBC through submission of an rDNARD is recommended. These experiments include:

- Those synthetic nucleic acids that: (1) can neither replicate nor generate nucleic acids that can replicate in any living cell (e.g., oligonucleotides or other synthetic nucleic acids that do not contain an origin of replication or contain elements known to interact with either DNA or RNA polymerase), and (2) are not designed to integrate into DNA, and (3) do not produce a toxin that is lethal for vertebrates at an LD50 of less than 100 nanograms per kilogram body weight. If a synthetic nucleic acid is deliberately transferred into one or more human research participants and meets the criteria of Section III-C, it is not exempt under this section.
- Those that are not in organisms, cells, or viruses and that have not been modified or manipulated (e.g., encapsulated into synthetic or natural vehicles) to render them capable of penetrating cellular membranes.
- Those that consist solely of the exact recombinant or synthetic nucleic acid sequence from a single source that exists contemporaneously in nature.
- Those that consist entirely of nucleic acids 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.

- Those that consist entirely of nucleic acids from a 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).
- 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 will be prepared and periodically revised by the NIH Director with advice of the RAC after appropriate notice and opportunity for public comment. See Appendices A-I through A-VI, Exemptions under Section III-F-6--Sublists of Natural Exchangers, of the *NIH Guidelines* for a list of natural exchangers that are exempt.
- Those genomic DNA molecules that have acquired a transposable element, provided the transposable element does not contain any recombinant and/or synthetic DNA.
- Those that do not present a significant risk to health or the environment (see Section IV-C-1-b-(1)-(c) of the *NIH Guidelines*) as determined by the NIH Director, with the advice of the RAC, and following appropriate notice and opportunity for public comment. See also Appendix C of the *NIH Guidelines*.

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VII Procedures for Initial Registration of Experiments Involving rDNA

When a PI initiates a new project and completes a Division of Sponsored Program (DSP) Proposal Routing Form, s/he will indicate on the Routing Form that the proposed project involves rsNAM, when applicable. DSP will generate a follow-up notification to the PI to serve as a reminder that IBC approval may be required; links to the electronic rDNARD and the *NIH Guidelines* are included in the notification. Environmental Health & Safety (EHS)'s Biosafety Office receives a copy of the notification to the PI and will ensure there is follow up. When rsNAM research is covered by the *NIH Guidelines*, the PI must complete the electronic rDNARD and submit it to the Biosafety Office. The Biosafety Office will process the rDNARD for IBC review (See Section VIII). An on-site audit will be performed annually in the laboratory of each PI whose proposed rsNAM research must be conducted at Biosafety Level 2 or higher; if the PI has not been audited previously, an initial audit will be scheduled at the time the rDNARD is submitted.

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VIII IBC Process for Review of rDNA Registration Documents

a. Protocols not involving human research participants

The Biosafety Office will review all newly submitted rDNARDs for completeness and if necessary, request additional information from the PI. If the requested information is provided in adequate

time, the rDNARD will be re-reviewed, and if appropriate, included in the agenda for the next IBC meeting. Completed rDNARDs will be moved into the "Committee Review" section of the online registration program. One week prior to the IBC meeting, committee members will receive an automated e-mail that includes a hyperlink to each pending completed rDNARD. IBC meetings will be held every two weeks.

Each rDNARD requires IBC action by a majority vote of the members attending a meeting in one of the following ways: approved, disapproved or tabled. If an IBC member has a conflict of interest, as defined by University policy, s/he must make the conflict known and recuse him/herself from the consideration of that protocol. Members unable to attend a meeting may submit comments or concerns on pending rDNARDs to the Biosafety Office prior to the meeting; during the scheduled meeting, comments or concerns so submitted will be read to the members in attendance. For each rDNARD approved by the IBC, the Biosafety Office will change the status of the rDNARD to "approved" and an automated e-mail will be sent to the PI, Co-PIs, and authorized users, as appropriate. The approved rDNARD, accessible through the online registration program, will bear the approval date and the expiration date. If a majority of IBC members in attendance determines that additional information is needed for a pending rDNARD and for this reason votes to table the document, the following procedure will be used:

1. The Biosafety Office or the IBC Chair will send to the PI a request for the additional information no later than two business days after the IBC meeting. The request will indicate the date of the next protocol submittal to the IBC and the PI will be advised to provide a written response containing the additional information at least two days prior to that date. This written response may take the form of a comment or, if appropriate, a revised rDNARD that includes the requested additional information.
2. Upon receipt of a response from the PI, it will be forwarded to the IBC members at least one week prior to the next scheduled meeting and the rDNARD in question will be included in the list of rDNARDs that will be considered at that meeting.
3. If the PI does not respond by the requested date, the Biosafety Office or the IBC Chair will send a second request to the PI. This request will indicate the date of the next scheduled IBC meeting at which the rDNARD would be reconsidered and the PI will be advised to provide to the IBC Chair a written response at least one week prior to that date. If the PI does not respond to the second request for additional information, the rDNARD will be withdrawn from consideration and will be returned to the PI.
4. Based upon the PI's response to the request for additional information, the IBC will approve, disapprove, or table the rDNARD by majority vote of the members in attendance. If the IBC deems the PI's response to its request for additional information as inadequate, the committee will request the PI amend the written response or attend the next IBC meeting.
5. At any point in the above procedure, an IBC member or the PI may request that the PI appear before the IBC, and such request will be honored.

b. Protocols involving human research participants

PIs must review Appendix M of the *NIH Guidelines* and prepare the required documentation for IBC and IRB review. The required documentation must be submitted, along with the online rDNARD, to the IBC. IBC review will include consideration of the following:

- Whether the protocol meets one or more of the following criteria and thus requires public RAC review: (1) If the protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience; (2) If the protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value; or (3) If the proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate the protocol rigorously.
- Inclusiveness of the informed consent document;
- Safety of the vectors used; and
- Risks to the patient given the vector used.

In collaboration with the IBC, the IRB will also render their opinion on whether the protocol warrants public RAC review and the two oversight bodies will send letters to the PI outlining this review. The PI must submit these letters, along with the documentation described in Appendix M, to NIH OSP in order to register their protocol with the Federal Government. If no oversight body requests public RAC review, the PI will receive documentation from the NIH that the initial protocol registration process is complete. If one or more oversight bodies requests public RAC review and the NIH agrees that such review is warranted, the PI will receive a letter from the NIH summarizing the RAC's comments and recommendations, if any.

The PI will submit either the NIH protocol registration document or the RAC's comments and recommendations to the IBC for final protocol review. The PI will be notified through e-mail when their rDNARD is approved by the IBC; copies of approved rDNARDs will be sent to the IRB Office with notification that the protocol was approved. PIs will have access to the electronically signed document for their files and to use in providing copies to granting/regulatory agencies. Only after the NIH protocol registration process, receipt of IRB and IBC approvals, and all applicable regulatory authorizations have been obtained, can research participants be enrolled in the human gene transfer experiment.

c. Experiments that might be considered "Dual Use Research of Concern" (DURC)

IBC members will evaluate the proposed experiments using the US Government Policy's[1] seven classes of dual use experiments involving rsNAM to determine if the experiments proposed meet DURC criteria. Any IBC member may request that a vote be taken on whether the experiments proposed in an rDNARD under consideration meet these criteria. If a majority of the members in attendance vote that the proposed experiments do not meet DURC criteria, the standard procedure for review of rDNARDs will be followed. If a majority of the members in

attendance vote that the proposed experiments meet DURC criteria, the rDNARD must first be considered and approved by a majority vote of the IBC. No later than one week after IBC approval, the IBC Chair will send a copy of the rDNARD along with a letter outlining the IBC members' reasons for deciding that the proposed experiments meet DURC criteria to the Asst. VPR for further consideration.

[1]United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern

d. Documents relating to the University's regulation of rsNAM

IBC meeting minutes will be transcribed by Biosafety Office staff, reviewed, revised and approved by the IBC Chair, and distributed to all members. All documents relating to the University's regulation of rsNAM, including but not limited to submitted rDNARDs, IBC meeting minutes, and correspondence with research staff, will be maintained within the electronic database, or where appropriate, kept on file in the Biosafety Office.

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IX IBC Annual Review / Annual Reporting of Approved Protocols

Approved DNARDs will be reviewed annually for two years and expire three years after initial approval. Eleven months after initial approval, and again one year and 11 months hence, a notification will be sent to the PI by the Biosafety Office with a request that s/he review the approved project. The PI must reply by return email, marking one of the following responses:

- the project is inactive;
- the project no longer involves rsNAM;
- the project is active, no changes; or
- the project is active and changes are anticipated, e.g., changes in personnel involved in the research or an amendment has been submitted for changes involving inserts/vector/hosts (the changes must be specified).

The date of the PI's review and response will be entered into the electronic rDNA database. If the project is inactive or no longer involves rsNAM, the related information in the database will be archived, thereby precluding additional review cycles. When a PI indicates that changes, as listed above, are planned, the changes may be approved administratively (changes in personnel), approved by the IBC Chair (minor amendment) or approved following full committee review (major amendment). See Section X, Amendments to rDNARDs, for information on requesting amendments and the approval process.

Two years and 11 months after initial approval, a notification will be sent to the PI stating that the project is expiring and can only be renewed by submitting a newly-completed rDNARD. The PI must reply and indicate that the project is complete or, if the research is to continue, a new rDNARD will be submitted.

Investigators who have protocols involving human subjects must comply with annual data reporting requirements. Information submitted in these annual reports will be evaluated by NIH OSP, and possibly considered at a future RAC meeting. A copy of the annual data report should be sent to Haley Sinn, Biological Safety Officer, Environmental Health & Safety.

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X Amendments to rDNARDs

To initiate an amendment request to an approved rDNARD, the PI or authorized user must access their protocol online and amend in the proposed changes; changes to the insert/vector/host table should be highlighted in order to facilitate review and record keeping. The BSO will process amendment requests on a case-by-case basis to ensure that the appropriate review process is followed. Minor amendments, e.g., the addition of a co-PI, addition/change to a vector requiring the same BSL, use of a less or equally hazardous cell line, or adding a non-pathogenic host such as an *E. coli* K-12 strain, can be approved by the IBC Chair without full committee review. If the IBC Chair agrees that the changes are appropriate for a minor amendment and approves them as such, an email notification will be sent to the PI, authorized users and Biosafety Office. Major amendments, e.g., increase in assigned BSL/ABSL, the addition of animals, or a change in the scope of the project, will be sent to the full IBC to be reviewed at the next regularly scheduled meeting. Requests to add or delete personnel to an approved rDNARD will be processed administratively without IBC Chair involvement; prior to approval, administrative staff will ensure that all online training is complete for added personnel.

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XI Reporting of Adverse Events

Investigators involved in human gene transfer protocols must report any serious adverse event (SAE) to the local IRB, IBC and NIH OSP. The requirements for reporting SAEs in human gene transfer research are found in Appendix M of the *NIH Guidelines*; a reporting template is available through NIH OSP. Reporting SAEs through the HAWK-IRB system will inform the Director of EHS and the BSO through an automated email notification. The BSO will forward the information to the IBC Chair and IBC for discussion, if appropriate. The PI must report events that are unexpected and possibly associated with the gene transfer product to OSP within 15 calendar days of sponsor notification, unless they are fatal or life threatening, in which they must be reported within 7 calendar days.

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XII Process for Reporting Violations of the *NIH Guidelines*

Allegations regarding a violation of the *NIH Guidelines* could be identified through at least two routes: (1) a whistleblower: student, staff, or faculty who in good faith reports real or perceived University-related misconduct (see the anti-retaliation policy for reporting of misconduct in research) or (2) through the job duties of Biosafety staff. When Biosafety staff are made aware that a violation of the *NIH Guidelines* may have occurred, staff will make reasonable efforts to inquire further about the credibility of such information. The BSO will notify the IBC Chair, the Institutional Official (IO) and the EHS Director of credible information. If the IBC Chair, IO and EHS Director agree to proceed with an investigation, the BSO will provide the PI with written notice of the allegation and the plans for an investigation. Upon completion of the investigation, the BSO will send a report to the IBC Chair, the IO, and the EHS Director. If after careful review of the investigation report, a majority of these persons opines that the findings reasonably support the allegation of a violation, the report will be sent to the members of the IBC for review. The BSO will notify NIH OSP of incidents requiring immediate reporting through email; NIH OSP's Incident reporting template will be used to draft the report.

The investigation report will be considered at a meeting of the IBC convened for that purpose, or at a previously scheduled meeting if one will occur shortly after the report is sent to the IBC members. After consideration of the report, written materials submitted by the PI, if any, and the information presented in person by the PI, if any, the members in attendance will determine by majority vote if a violation of the *NIH Guidelines* has occurred. If the IBC determines that a violation has occurred, the IBC Chair will prepare a violation report to be sent to NIH OSP that will outline the investigation and any corrective actions to reduce the likelihood of the occurrence of such violations in the future. Alternatively, the IBC Chair may ask the PI if s/he wishes to prepare the violation report, as specified in the *NIH Guidelines*. If the PI chooses to prepare said report, the IBC Chair will provide guidance in its preparation. If the IBC Chair deems the report prepared by the PI to be unacceptable, the IBC Chair will prepare his/her own report. Independent of who prepares the violation report, the IBC Chair will ensure that it is sent to NIH OSP within 30 days of the Biosafety Office's becoming aware of the violation; copies of the violation report will be sent to the IO and to the PI.

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