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COMS Protocol Review Policy

I. Purpose

COMS reviews and approves research at Harvard University and its affiliates that involves COMS-Regulated Materials ("CRM") as defined in the Policy Introduction (II) Scope.

II. Applicability

Any COMS application that is approved by the committee must follow the guidance of this policy and the recommendations in the NIH Guidelines Section III: Experiments Covered by NIH Guidelines.

III. Implementation Procedures

A. Review Procedure for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

Research involving recombinant or synthetic nucleic acid molecules is covered under one of six sections (Sections III-A through III-F) of the National Institutes of Health (NIH) Guidelines for the Use of Recombinant DNA Molecules (NIH Guidelines). The review process differs depending on which section the research falls under. The Principal Investigator (PI) is responsible for submitting the completed and signed COMS protocol document to their institutional biosafety officer (BSO). The protocol document requires the PI to make an initial determination of which section of the NIH Guidelines (if any) their research falls under. The BSO then conducts a risk assessment and verifies the PI's initial determination of the NIH Guideline section is correct. If the BSO risk assessment results in the protocol requiring further review due to diversity of laboratory activities, common laboratory areas, or other concerns, appointed committee review may be needed. Further information may be provided in the BSO risk assessment.

1. NIH Section III-A
    a. Experiments Covered
    b. Experiments that involve 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 humans, veterinary medicine, or agriculture, will be reviewed by RAC."

c. Consideration should be given as to whether the drug resistance trait to be used in the experiment would render that microorganism resistant to the primary drug available to and/or indicated for certain populations, for example children or pregnant women.

d. At the request of COMS, NIH/OSP will make a determination regarding whether a specific experiment involving the deliberate transfer of a drug resistance trait falls under Section III-A-1-a and therefore requires RAC review and NIH Director approval. An Institutional Biosafety Committee may also consult with NIH/OSP regarding experiments that do not meet the requirements of Section III-A-1-a but nonetheless raise important public health issues. NIH/OSP will consult, as needed, with one or more experts, which may include the RAC.

2. Risk Assessment

   a. The institutional BSO will conduct a risk assessment of the proposed research. See the Risk Assessment policy. The results of the risk assessment will include:

      - Recommended biosafety level;
      - Containment: The containment, procedures and, if necessary, additional stipulations for the protocol. If available, agent-specific guidance, e.g. risk group or biosafety level, from the NIH Guidelines, CDC/NIH BMBL, or Public Health Agency of Canada Pathogen Safety Data Sheets.

3. Committee Review

   a. Protocols that fall under Section III-A, will be assigned at least one committee member reviewer and discussed at an upcoming COMS meeting.

b. Protocol initiation requires review by the NIH Recombinant DNA Advisory Committee (RAC) and approval by COMS and the NIH Director.
c. Once appropriate review has been obtained and after discussion at a COMS meeting, the COMS Office will send an approval letter signed by the COMS Chair to the PI indicating that work is approved under the biosafety level and stipulations indicated in the letter.

4. NIH Section III-B
   a. Experiments Covered (Require NIH/ OSP and Institutional Biosafety Committee Approval Before Initiation):

      Section III-B-1: Experiments that involve the "deliberate formation of recombinant or synthetic nucleic acid molecules containing genes for the biosynthesis of toxin molecules lethal for vertebrates at an LD50 of less than 100 nanograms per kilogram body weight (e.g., microbial toxins such as the botulinum toxins, tetanus toxin, diphtheria toxin, and *Shigella dysenteriae* neurotoxin)."

      Section III-B-2: Experiments that have been Approved (under *Section III-A-1-a*) as Major Actions under the NIH Guidelines***:*** Upon receipt and review of an application from the investigator, NIH OSP may determine that a proposed experiment is equivalent to an experiment that has previously been approved by the NIH Director as a Major Action, including experiments approved prior to implementation of these changes. An experiment will only be considered equivalent if, as determined by NIH OSP, there are no substantive differences and pertinent information has not emerged since submission of the initial III-A-1-a experiment that would change the biosafety and public health considerations for the proposed experiments. If

such a determination is made by NIH OSP, these experiments will not require review and approval under Section III-A.

b. Risk Assessment

i. The institutional BSO will conduct a risk assessment of the proposed research. See the Risk Assessment policy. The results of the risk assessment will include:

- Recommended biosafety level;
- Containment: The containment, procedures and, if necessary, additional stipulations for the protocol. If available, agent-specific guidance, e.g. risk group or biosafety level, from the NIH Guidelines, CDC/NIH BMBL, or Public Health Agency of Canada Pathogen Safety Data Sheets.

c. Committee Review

i. Applications that fall under Section III-B will be assigned at least one committee member reviewer and discussed at an upcoming COMS meeting. Protocol initiation requires approval by the NIH Office of Science Policy (OSP) and COMS.

ii. Once appropriate review has been obtained, after discussion at a COMS meeting, the COMS Office will send an approval letter signed by the COMS Chair to the PI indicating that work is approved under the biosafety level and stipulations indicated in the letter.

5. NIH Section III-C (i.e. human gene therapy clinical trials)

a. Experiments Covered

Clinical trials that involve the deliberate transfer into human research participants of either:

i. Recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules; or

ii. 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.

b. Risk Assessment

i. The BSO is responsible for providing COMS will all relevant trial information and providing an overview of the trial at the COMS meeting.

c. Committee Review

i. Applications that falls under Section III-C will be assigned at least one committee member reviewer and discussed at an upcoming COMS meeting.

ii. Protocol initiation requires approval by COMS and the local Institutional Review Board (IRB). For some protocols, review by the NIH RAC may also be required. (See Clinical Trial policy for additional information.) All material relating to clinical studies must be submitted to the COMS Office of Biological Safety six weeks prior to the next COMS meeting. Local institutional deadlines vary. PIs/ Clinical Coordinators should consult with their institutional biosafety officer for their local institutional deadline. All human gene therapy studies require two scientific appointed reviewers. Non-recombinant or Synthetic nucleic acid COMS Regulated Materials ("CRM"), as defined in the Policy Introduction (II) Scope, require a minimum of one scientific

appointed reviewer. The COMS Chair may request an additional reviewer.

iii. The protocol will be discussed at an upcoming COMS meeting.

iv. After discussion at a COMS meeting, the COMS Office will send an approval letter signed by the COMS Chair to the PI indicating that work is approved under the biosafety level and stipulations indicated in the letter.

6. NIH Section III-D

a. Experiments Covered:

i. Experiments that involve the introduction of recombinant or synthetic nucleic acid molecules into Risk Group 2 agents (or higher);

ii. Experiments in which DNA from Risk Group 2 or Risk Group 3 agents is transferred into nonpathogenic prokaryotes or lower eukaryotes;

iii. 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;

iv. Experiments involving whole animals in which the animal's genome has been altered by stable introduction of recombinant or synthetic nucleic acids, or DNA or RNA molecules derived there from, into the germ-line (transgenic animals) and experiments involving viable recombinant DNA-modified microorganisms tested on whole animals;

v. Experiments to genetically engineer plants by recombinant DNA methods where BL3-P containment is recommended;

vi. Experiments Involving More than 10 Liters of Culture; and

vii. Experiments with some strains of influenza viruses generated by recombinant methods.

b. Risk Assessment
    i. The institutional BSO will conduct a risk assessment of the proposed research. See the Risk Assessment policy. The results of the risk assessment will include:
        - Recommended biosafety level;
        - Containment: The containment, procedures and, if necessary, additional stipulations for the protocol. If available, agent-specific guidance, e.g. risk group or biosafety level, from the NIH Guidelines, CDC/NIH BMBL, or Public Health Agency of Canada Pathogen Safety Data Sheets; and
        - If necessary, a recommendation for appointed committee member review
c. Committee Review
    i. If the Institutional BSO, Director of COMS, or the COMS Chair recommends appointed committee member review, at least one committee member reviewer will be assigned..
    ii. The protocol will be discussed at an upcoming COMS meeting.
    iii. After discussion at a COMS meeting, the COMS Office will send an approval letter signed by the COMS Chair to the PI indicating that work is approved under the biosafety level and stipulations indicated in the letter.

7. NIH Section III-E
    a. Experiments Covered
        i. Experiments involving the formation of recombinant DNA molecules containing no more than two-thirds of the genome of any eukaryotic virus;
        ii. Experiments involving recombinant DNA-modified whole plants, and/or experiments involving recombinant DNA-

modified organisms associated with whole plants where BL2-P or lower containment is recommended; and

iii. Experiments involving the generation of rodents in which the animals' genomes have been altered by stable introduction of recombinant DNA, or DNA derived there from, into the germ-line (transgenic rodents).

b. Risk Assessment

i. The institutional BSO will conduct a risk assessment of the proposed research. See the Risk Assessment policy. The results of the risk assessment will include:

- Recommended biosafety level;
- Containment: The containment, procedures and, if necessary, additional stipulations for the protocol. If available, agent-specific guidance, e.g. risk group or biosafety level, from the NIH Guidelines, CDC/NIH BMBL, or Public Health Agency of Canada Pathogen Safety Data Sheets; and
- If necessary, a recommendation for appointed committee member review.

c. Committee Review

i. If the Institutional BSO, Director of COMS, or the COMS Chair recommends appointed committee member review, at least one committee member reviewer will be assigned and the protocol will be discussed at an upcoming COMS meeting.

ii. If appointed committee member review is not recommended, the BSO will verify that III-E is the appropriate section of the Guidelines. The BSO will email the PI that the work under section III-E may commence under the biosafety level and stipulations indicated by the BSO. The protocol will be reviewed at an upcoming COMS meeting.

iii. After discussion at a COMS meeting, the COMS Office will send an approval letter signed by the COMS Chair to the PI indicating that work is approved under the biosafety level and stipulations indicated in the letter.

8. NIH Section III-F
    a. Experiments Covered
        i. Experiments involving the use of recombinant or synthetic nucleic acid molecules that are exempt from the NIH Guidelines. However, other federal and state standards of biosafety may still apply to such research (for example, the Centers for Disease Control and Prevention (CDC)/NIH publication Biosafety in Microbiological and Biomedical Laboratories). The following Sections III F 1 through 8 outline the exemptions under the NIH Guidelines:
            - Section III-F-1. 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;
            - Section III-F-2. 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;

- Section III-F-3. Those that consist solely of the exact recombinant or synthetic nucleic acid sequence from a single source that exists contemporaneously in nature;
- Section III-F-4. 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;
- Section III-F-5. 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);
- Section III-F-6. 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 Section IV-C-1-b-(1)-(c), *Major Actions)*;
- Section III-F-7. Those genomic DNA molecules that have acquired a transposable element, provided the transposable element does not contain any recombinant and/or synthetic DNA; and

- Section III-F-8. Those that do not present a significant risk to health or the environment (see Section IV-C-1-b-(1)-(c), *Major Actions*), as determined by the NIH Director, with the advice of the RAC, and following appropriate notice and opportunity for public comment.

b. Risk Assessment

i. The institutional BSO will conduct a risk assessment of the proposed research. (See Risk Assessment policy). The results of the risk assessment will include:

- Recommended biosafety level;
- Containment: The containment, procedures and, if necessary, additional stipulations for the protocol. If available, agent-specific guidance, e.g. risk group or biosafety level, from the NIH Guidelines, CDC/NIH BMBL, or Public Health Agency of Canada Pathogen Safety Data Sheets; and
- If necessary, a recommendation for appointed committee member review

c. Committee Review

i. If the Institutional BSO, Director of COMS, or the COMS Chair recommends appointed committee member review, at least one committee member reviewer will be assigned and the protocol will be discussed at an upcoming COMS meeting.

ii. If appointed committee member review is not recommended, the BSO and the Director of COMS will verify that III-F is the appropriate section of the Guidelines.

iii. The COMS Office will send an approval letter signed by the COMS Chair to the PI indicating that work is approved

under the biosafety level and stipulations indicated in the letter.

B. Review Procedure for Research Not Involving Recombinant or Synthetic Nucleic Acid Molecules

Research not involving recombinant or synthetic nucleic acid molecules is covered under the definition of CRM (see Policy Introduction (II) Scope). The review process is dependent on the risk assessment conducted by the institutional BSO and input from the Director of COMS and the COMS Chair.

1. Bacteria, Viruses, Fungi, Parasites and Prions that are not regulated by OSP
    a. Experiments Covered
        i. Experiments involving the use of non-recombinant CRM, regardless of their pathogenicity to humans.
    b. Risk Assessment
        i. The institutional BSO will conduct a risk assessment of the proposed research. See the Risk Assessment policy. The results of the risk assessment will include:
            - Recommended biosafety level;
            - Containment: The containment, procedures and, if necessary, additional stipulations for the protocol. If available, agent-specific guidance, e.g. risk group or biosafety level, from the NIH Guidelines, CDC/NIH BMBL, or Public Health Agency of Canada Pathogen Safety Data Sheets;
            - Agent-specific, procedure-relevant COMS precedent; and
            - If necessary, a recommendation for appointed committee member review.
    c. Committee Review
        i. If the application involves the use of Select Agents (as defined by the HHS and USDA) and/or the containment recommendation is biosafety level 3, then the application will be assigned at least one

committee member reviewer and presented at an upcoming COMS meeting.

ii. If the application does not involve the use of Select Agents or BL3 containment:

- The Institutional BSO, Director of COMS, or the COMS Chair may recommend appointed committee member review, at which time at least one committee member reviewer will be assigned and the protocol will be discussed at an upcoming COMS meeting.
- If appointed committee member review is not recommended, the BSO will verify that the protocol does not involve recombinant or synthetic nucleic acid molecules. The BSO will email the PI that the work may commence immediately under the biosafety level and stipulations indicated by the BSO. The protocol will be discussed at an upcoming COMS meeting.
- After discussion at a COMS meeting, the COMS Office will send an approval letter signed by the COMS Chair to the PI indicating that work is approved under the biosafety level and stipulations indicated in the letter.

2. Human or nonhuman primate blood, cells, tissues, fluids, or secretions

a. Experiments Covered

i. Experiments involving the use of human or nonhuman primate blood, cells, tissues, fluids, or secretions.

b. Risk Assessment

i. The institutional BSO will conduct a risk assessment of the proposed research. See the Risk Assessment policy. The results of the risk assessment will include:

- Recommended biosafety level;
- Containment: The containment, procedures and, if necessary, additional stipulations for the protocol. If

available, agent-specific guidance, e.g. risk group or biosafety level, from the NIH Guidelines, CDC/NIH BMBL, or Public Health Agency of Canada Pathogen Safety Data Sheets; and

- If necessary, a recommendation for appointed committee member review.

c. Committee Review

i. The Institutional BSO, Director of COMS, or the COMS Chair may recommend appointed committee member review; the protocol will be discussed at an upcoming COMS meeting.

ii. If appointed committee member review is not recommended, the BSO and the Director of COMS will verify that the protocol does not contain recombinant or synthetic nucleic acid molecules.

iii. The COMS Office will send an approval letter signed by the COMS Chair to the PI indicating that work is approved under the biosafety level and stipulations indicated in the letter.

3. Biological toxins subject to the Federal Select Agent Program

a. Experiments Covered

i. Experiments involving the use of biological toxins subject to the Federal Select Agent Registry Program.

b. Risk Assessment

i. The institutional BSO will conduct a risk assessment of the proposed research. See the Risk Assessment policy. The results of the risk assessment will include:

- Recommended biosafety level;
- Containment: The containment, procedures and, if necessary, additional stipulations for the protocol. If available, agent-specific guidance, e.g. risk group or biosafety level, from the NIH Guidelines, CDC/NIH BMBL, or Public Health Agency of Canada Pathogen Safety Data Sheets;

- If necessary, a recommendation for appointed committee member review.

c. Committee Review

i. If the Institutional BSO, Director of COMS, or the COMS Chair recommends appointed committee member review, at least one committee member reviewer will be assigned.

ii. The protocol will be discussed at an upcoming COMS meeting.

iii. After discussion at a COMS meeting, the COMS Office will send an approval letter signed by the COMS Chair to the PI indicating that work is approved under the biosafety level and stipulations indicated in the letter.

IV. Policy Authority

The Committee on Microbiological Safety shall enforce this policy.

V. Related Policies

- COMS Risk Assessment Policy
- COMS Clinical Trial Policy

VI. References

- NIH Guidelines
- CDC/NIH BMBL 5th edition (see Table 2)
- CDC/USDA Select Agent Regulations