IMPLEMENTATION GUIDANCE

for the

United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential

May 2024

Implementation Guidance for the United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential

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LIST OF ABBREVIATIONS

BMBL: Biosafety in Microbiological and Biomedical Laboratories

BSAT: Biological Select Agents and Toxins

BSL: Biosafety Level

CDC: Centers for Disease Control and Prevention

DURC: Dual Use Research of Concern

FDA: Food and Drug Administration

FSAP: Federal Select Agent Program

HHS: Department of Health and Human Services

ICDUR: Institutional Contact for Dual Use Research

IRE: Institutional Review Entity

MCM: Medical Countermeasure

NIH: National Institutes of Health

NIH Guidelines: *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*

PEPP: Pathogen with Enhanced Pandemic Potential

PI: Principal Investigator

PPP: Pathogen with Pandemic Potential

The Policy: United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential

USDA: United States Department of Agriculture

For a list of definitions from Section 3 of the Policy, see Appendix D of this *Implementation Guidance*.

A. PURPOSE OF THE POLICY FOR OVERSIGHT OF DUAL USE RESEARCH OF CONCERN AND PATHOGENS WITH ENHANCED PANDEMIC POTENTIAL

The purpose of the United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential ("the Policy")[1] is to establish a unified federal oversight framework for conducting and managing certain types of federally funded life sciences research on biological agents and toxins that may pose risks to public health, agriculture, food security, economic security, or national security.

The Policy complements existing U.S. government statutes and regulations regarding biosafety and biosecurity oversight and the responsible conduct of life sciences research involving pathogens and toxins. The Policy is to be implemented consistent with all applicable laws and regulations; all legally binding treaties, commitments, and United Nations Security Council resolutions prohibiting the development and use of biological agents and toxins as weapons; and all relevant Presidential Directives and Executive Orders.

Research oversight is a critical component of effective biosafety and biosecurity practices and the responsible conduct of research involving biological agents and toxins. The intent of research oversight is to increase the awareness of researchers, institutions, and federal funding agencies about the biosafety and biosecurity concerns associated with certain types of research and to ensure that appropriate risk mitigation measures are in place to prevent biosafety incidents (e.g., unintended personal exposure or release of an agent outside of containment) or biosecurity incidents (e.g., theft or intentional misuse of information, knowledge, products, or technology). The Policy provides recommended precautionary measures to ensure that the potential benefits and the anticipated risks are identified and assessed, potential biosafety and biosecurity risks are mitigated, and research is carried out safely and securely. These measures should be applied in a manner commensurate with risk in order to minimize adverse impacts on research and preserve and foster the benefits of research.

The Policy supersedes the 2012 United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern (Federal DURC Policy), the 2014 United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern (Institutional DURC Policy), and the 2017 Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO). The Policy does not supersede, but complements, existing federal regulations,[2] including the Select Agent Regulations. This *Implementation Guidance* comprises a set of explanatory materials and tools designed to aid principal investigators (PIs), research institutions, institutional review entities (IREs), federal funding agencies, and other federal departments and agencies in implementation of the Policy.

[1] United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential (2024).

[2] If a PI or research institution has a question about the relationship between the research oversight framework under the Policy and any other federal program, they may contact the federal funding agency.

B. SCOPE OF POLICY OVERSIGHT

This part of the *Implementation Guidance* provides additional detail on the definitions and scope of Category 1 and Category 2 research oversight described in Section 4 of the Policy.

Table 1. Summary of Category 1 and Category 2 Research

Definitions and Scopes	Category 1 Research	Category 2 Research
Primary risk	The research can be reasonably anticipated to provide, or does provide, knowledge, information, products, or technologies that could be misapplied to do harm with no, or only minor, modification to pose a significant threat with potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security. Category 1 research may also have biosafety risks.	The research can be reasonably anticipated to result in the development, use, or transfer of a pathogen with enhanced pandemic potential (PEPP) or an eradicated or extinct pathogen with pandemic potential (PPP) that may pose a significant threat to public health, the capacity of health systems to function, or national security, through the potential accidental or deliberate introduction of a PEPP or an eradicated or extinct PPP into a human population. Category 2 research may also have dual use risks.
Types of pathogens in scope	• All Biological Select Agents and Toxins, as listed in 9 CFR 121.3–121.4, 42 CFR 73.3–73.4, and 7 CFR 331.3 and regulated by USDA and/or HHS • All Risk Group 4 pathogens listed in Appendix B of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules - Classification of Human Etiologic Agents on the Basis of Hazard (NIH Guidelines)*	• Any pathogen that is modified in such a way that is reasonably anticipated to result in the development, use, or transfer of a PEPP. This includes the development of new PPPs from non-PPPs as well as the enhancement of existing PPPs. • Eradicated or extinct PPPs that may pose significant threat to public health, the capacity of health systems to function, or national security

Definitions and Scopes	Category 1 Research	Category 2 Research
	• A subset of Risk Group 3 pathogens listed in Appendix B of the *NIH Guidelines*[3] • For biological agents affecting humans that have not been assigned a Risk Group in the *NIH Guidelines*, agents affecting humans that are recommended to be handled at Biosafety Level 3 (BSL-3) or Biosafety Level 4 (BSL-4) per the BMBL guidance are subject to this Policy.[4]	
Types of experimental outcomes in scope	Nine experimental outcomes outlined in Section 4.1.2 of the Policy	Four experimental outcomes outlined in Section 4.2.2 of the Policy
Level of federal review	Funding agency review	Funding agency and department-level review[5]

[3] Note: As of the time of release of this Policy, this subset consists of all RG3 pathogens except HIV, HTLV, SIV, Mtb (including mycobacterium bovis), Clade II of MPVX viruses unless containing nucleic acids coding for clade I MPVX virus virulence factors, vesicular stomatitis virus, Coccidioides immitis, C. posadasii, Histoplasma capsulatum, and H. capsulatum var. duboisii. This list may be updated in the Implementation Guidance on a periodic basis. Beyond this list, as stated in Section 6.2, this Policy also provides voluntary guidance to PIs and research institutions for research that is outside of the scope of this Policy but that may pose potential risk and may warrant oversight and risk mitigation at the institutional level.

[4] Note: In the event no risk group or Biosafety Level has been assigned to an agent, for example in the case of a newly emerging pathogen or chimeric agent, the appropriate institutional body should perform a risk assessment to determine the appropriate Biosafety Level for handling the agent, given the experimental protocol being proposed. The assessment should take into account known properties of the agent and similarities to existing agents. Such agents requiring handling at BSL-3 or BSL-4 are biological agents under Section 4.1.1 of this Policy.

[5] In some cases, the federal funding agency and the department funding an in-scope research study are distinct (e.g., the National Institutes of Health and the Department of Health and Human Services). In other cases, they are the same (e.g., the National Science Foundation). Federal departments and agencies will implement this Policy based on their specific departmental structure.

B.1 Definition and Scope of Category 1 Oversight

B.1.1 Definition: Dual Use Research of Concern

Dual use research of concern (DURC) as defined in the Policy is "life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be misapplied to do harm with no, or only minor, modification to pose a significant threat with potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security."

B.1.2 Research Subject to Category 1 Oversight

Research that is subject to Category 1 oversight must meet the following three criteria:

- Involves one or more of the biological agents or toxins within scope of Section 4.1.1 of the Policy;

- Is reasonably anticipated to result, or does result, in one or more of the experimental outcomes listed in Section 4.1.2 of the Policy; and

- Based on current understanding, the research institution and/or federal funding agency assesses that the research constitutes DURC, as specified in Section 4.1.3 of the Policy.

The Policy supersedes the Federal DURC Policy and Institutional DURC Policy, expands the scope of biological agents and toxins, and refines the list of experimental outcomes. The expanded scope of biological agents and toxins is based upon the recognition that additional biological agents and toxins, when manipulated in certain ways, have the potential to negatively impact public health, agriculture, food security, economic security, or national security.

This *Implementation Guidance* includes a checklist of all biological agents and toxins outlined in Section 4.1.1 of the Policy as of the time of the release of the Policy (see Appendix C) to assist with identifying those studies most likely to require enhanced oversight. However, the U.S. government also recognizes that it is difficult to anticipate all possible DURC that requires enhanced oversight, and there may be additional types of research that do not involve the biological agents or toxins or experiments outlined in Section 4.1.1 and Section 4.1.2 of the Policy that could constitute DURC.

PIs and IREs are encouraged to remain vigilant to additional types of research with any biological agent or toxin, regardless of its Risk Group, where the biological agent or toxin is experimentally manipulated in a way that could meet the definition of DURC, and to develop and apply appropriate risk mitigation measures. The PI and IRE are best positioned to assess whether studies on biological agents or toxins beyond this list should be considered for additional risk mitigation measures because of the dual use risks they may pose. Advances in science and technology have the potential to present situations that are not anticipated in this *Implementation Guidance* and PIs and IREs are encouraged to seek additional guidance from federal funding agencies, as needed. PIs, IREs, and research institutions are encouraged

to voluntarily conduct analogous risk assessment and develop risk mitigation measures when designing and developing engineered biological systems for other applications, even though such mitigation measures are outside the scope of the Policy.

Table 2 provides examples of risks posed by each type of Category 1 research experimental outcome listed in Section 4.1.2 of the Policy that, when involving biological agents and toxins listed in Section 4.1.1 of the Policy, may meet the threshold for Category 1 research oversight. These examples are provided to illustrate the types of risks associated with each experimental outcome and may not represent the full range of possible risks.

Table 2. Examples of Potential Risks Posed by Category 1 Experimental Outcomes

Category 1 Experimental Outcomes	**Examples of Associated Risks**
i. Increase transmissibility of a pathogen within or between host species	• Creates a pathogen more transmissible than the wild-type pathogen such that it is able to transmit more efficiently in and among human, plant, or animal populations.
ii. Increase the virulence of a pathogen or convey virulence (i.e., the ability of a pathogen to cause disease) to a non-pathogen	• Creates a pathogen more virulent than the wild-type pathogen, resulting in higher morbidity or mortality in human, plant, or animal populations.
iii. Increase the toxicity of a known toxin or produce a novel toxin	• Creates a toxin that causes morbidity or mortality comparable to its natural form at lower doses or creates a toxin that causes higher morbidity or mortality at similar doses comparable to its natural form. • Creates a new toxin, not found in nature, for which there is limited knowledge on how to detect, mitigate, or respond.
iv. Increase the stability of a pathogen or toxin in the environment, or increase the ability to disseminate a pathogen or toxin (e.g., improving characteristics of the pathogen or toxin such as environmental stability and ability to be aerosolized)	• Renders a pathogen or toxin with the ability to retain or increase its infectiousness or toxicity outside a living system. • Creates a pathogen or toxin that can be more effectively delivered via aerosolization, or enables novel aerosolization in a pathogen or toxin that typically transmits by other means.

Category 1 Experimental Outcomes	Examples of Associated Risks
	• Enhances the environmental stability of a pathogen or toxin, thereby increasing ease of transmissibility or capability to cause disease. • Develops a method for producing or disseminating large quantities of a pathogen or toxin.
v. Alter the host range or tropism of a pathogen or toxin	• Alters the route of transmission of a pathogen or toxin to increase the ease and effectiveness by which a pathogen or toxin may be transmitted, thus having broad potential consequences to humans, animals, or plants. • Alters the host range of a pathogen or toxin, which could put specific populations of humans, plants or animals at risk that were not previously susceptible to a given pathogen or toxin (e.g., makes an avian pathogen infectious to and among mammals). • Alters tissue tropism of a pathogen or toxin resulting in more severe disease manifestation in humans, plants, or animals (e.g., a respiratory pathogen's ability to become neurotropic). Note: Importantly, this type of experimental outcome is specifically for modifications to the pathogen or toxin and does not include the use of model systems in which there is broader or ubiquitous infection due to overexpression or differential expression of the cellular receptor.
vi. Decrease the ability for a human or veterinary pathogen or toxin to be detected using standard diagnostic or analytical methods	• Alters a pathogen or toxin such that it is no longer identifiable by widely used diagnostic tests or other detection modalities. • Alters the nucleic acid sequence of a pathogen or toxin in a way that preserves function but renders the pathogen or toxin no longer identifiable by screening

Category 1 Experimental Outcomes	Examples of Associated Risks
	mechanisms designed to detect nucleic acid sequences of concern.[6] Note: This type of experimental outcome is only applicable for human and veterinary Category 1 pathogens.
vii. Increase resistance of a pathogen or toxin to clinical and/or veterinary prophylactic or therapeutic interventions (e.g., antimicrobials, antivirals, antitoxins, vaccines)	• Alters a pathogen or toxin such that it causes disease which is not treatable, or severely increases the failure risk with extant therapeutics. • Modifies (i.e., a non-naturally occurring mutation) a pathogen or toxin such that it becomes newly resistant to multiple antimicrobials, antivirals, or antitoxins. • Creates a pathogen or toxin for which existing prophylactic measures available to the general population, such as vaccines, are no longer effective at preventing disease or transmission. Note: This type of experimental outcome is only applicable for human and veterinary Category 1 pathogens.
viii. Alter a human or veterinary pathogen or toxin to disrupt the effectiveness of pre-existing immunity, via immunization or natural infection, against the pathogen or toxin	• Modifies the antigenic profile of a pathogen or toxin such that it is less efficiently or no longer recognized via pre-existing immunity, thereby rendering humans or animals vulnerable to diseases from which they might otherwise have been protected. Note: This type of experimental outcome is only applicable for human and veterinary Category 1 pathogens.
ix. Enhance the susceptibility of a host population to a pathogen or toxin	• Generates a pathogen or toxin with an enhanced or a new ability to compromise immune responses of

[6] Sequences of concern are defined in "Screening Framework Guidance for Providers and Users of Synthetic Nucleic Acids," October 2023. https://aspr.hhs.gov/legal/synna/Documents/SynNA-Guidance-2023.pdf; and "Framework for Nucleic Acid Synthesis Screening," April 2024. https://www.whitehouse.gov/wp-content/uploads/2024/04/Nucleic-Acid_Synthesis_Screening_Framework.pdf.

Category 1 Experimental Outcomes	Examples of Associated Risks
	individuals or populations, thereby enabling the increased spread of disease. • Creates a pathogen or toxin that suppresses the host's immune response, resulting in increased morbidity or mortality.

B.2 Definitions and Scope of Category 2 Oversight

B.2.1 Definition #1: Pathogen with Pandemic Potential (PPP)

A pathogen with pandemic potential (PPP) as defined in the Policy is a "pathogen that is likely capable of wide and uncontrollable spread in a human population and would likely cause moderate to severe disease and/or mortality in humans."

A pathogen's capability for "wide and uncontrollable spread in a human population" is a function of the pathogen's ability to spread in a human population through an efficient means of transmission (e.g., via aerosol, respiratory droplets, direct contact, fomites, etc.). As a general benchmark, "wide and uncontrollable spread" typically refers to pathogens expected to exhibit sustained human-to-human transmission in a population under specific conditions, or an effective reproductive number (R_t) greater than one. Conditions that aid wide and uncontrollable spread include a relative lack of pre-existing population immunity to the pathogen, environmental stability of the pathogen, respiratory route of transmission, and lack of availability of or access to non-medical and medical countermeasures (MCMs) to contain the pathogen. Once a population has been exposed to a pathogen over multiple years or seasonal cycles, the ability for that pathogen to spread disease throughout the human population and cause moderate to severe disease in humans may diminish. However, the absence of one of these conditions alone is insufficient to rule out pandemic potential. For example, Influenza A virus subtype H1N1 (1918) is considered to have pandemic potential because it may be able to spread widely in a population despite the existence of MCMs.

A pathogen's capability to cause "moderate to severe disease and/or mortality in humans" may be estimated by comparing case hospitalization rate (CHR) and/or case fatality rates (CFR). These comparisons may not be clear-cut or relevant in every circumstance, but rather can provide a high-level guideline to help PIs, IREs, and federal funding agencies assess which pathogens are included and excluded from the PPP definition.

While R_t, CHR, and CFR are key tools for determining whether a pathogen is a PPP, it is important to note that these metrics can vary widely based on a range of factors (e.g., levels of population immunity, access to health care, community behaviors, etc.), and relevant data on these metrics may not be available for many pathogens under study in the laboratory. Other pathogen characteristics for determining moderate to severe disease potential may include types of symptoms, duration of disease, or long-term symptoms that persist after infection.

Classification of a pathogen as a PPP can evolve over time, including during the course of a pandemic, due to changing levels of population immunity, development of MCMs, and emergence of variants with differing levels of transmissibility and pathogenicity. Cumulatively, these metrics are meant to help broadly establish a reference class of pathogens that fit in the PPP definition, to help PIs, IREs, and federal funding agencies determine whether a particular pathogen fits the PPP definition based on what is known about the transmissibility and disease characteristics of that pathogen. For additional guidance on assessing the pandemic potential of a pathogen, refer to Part B.2.4.1 of this *Implementation Guidance*.

B.2.2 Definition #2: Pathogen with Enhanced Pandemic Potential (PEPP)

A pathogen with enhanced pandemic potential (PEPP) as defined in the Policy is "a type of PPP resulting from experiments that enhance a pathogen's transmissibility[7] or virulence, or disrupt the effectiveness of pre-existing immunity, regardless of its progenitor agent, such that it may pose a significant threat to public health, the capacity of health systems to function, or national security. Wild-type pathogens that are circulating in or have been recovered from nature are not PEPPs, but may be considered PPPs because of their pandemic potential."

"Progenitor agent" within the PEPP definition refers to the starting pathogen of the proposed experiment, which may be a PPP in its wild-type form or a pathogen that is not considered a PPP in its wild-type form, but that when modified meets the definition of a PEPP.

B.2.3 Definition #3: Eradicated or extinct PPP

Category 2 oversight is also required for experiments that generate, use, reconstitute, or transfer an eradicated or extinct PPP that may pose a significant threat to public health, the capacity of health systems to function, or national security, regardless of whether the experiment enhances the PPP. Current eradicated and extinct PPPs include Variola major and minor,[8] and Influenza A virus subtypes H1N1 (1918) and H2N2 (1957-1968). Any research with these PPPs is considered Category 2 because of the heightened consequences of biosafety or biosecurity incidents that could occur from directly handling or possessing such pathogens, even without any enhancement to virulence or transmissibility.

B.2.4 Research Subject to Category 2 Oversight

Research that is subject to Category 2 oversight must meet the following three criteria:

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[7] Experiments that enhance a pathogen's transmissibility (refers to Section 4.2.2 i of the Policy) include those that enhance environmental stability of the pathogen or change the tropism or host range of the pathogen in a way that enables an increased ability to infect humans.

[8] The Centers for Disease Control and Prevention (CDC) is one of only two World Health Organization (WHO) Collaborating Centers approved for Variola virus research in the world. All research using Variola virus at CDC is overseen by the WHO and required by the World Health Assembly resolution 52.10 to have immediate public health impact. The WHO Advisory Committee on Variola Virus Research reviews all research that is proposed by CDC each year. This review and risk assessment may be deemed by HHS as satisfying the review requirements outlined in the Policy for Category 2 research with Variola virus.

- Involves, or is reasonably anticipated to result in, a PPP as specified in Section 4.2.1 of the Policy;

- Is reasonably anticipated to result in, or does result in, one or more of the experimental outcomes or actions specified in Section 4.2.2 of the Policy; and

- Based on current understanding, the research institution, federal funding agency, and/or Departmental multidisciplinary review entity assesses that the research is reasonably anticipated to result in the development, use, or transfer of a PEPP or an eradicated or extinct PPP that may pose a significant threat to public health, the capacity of health systems to function, or national security as specified in Section 4.2.3 of the Policy.

PIs and IREs should also assess Category 2 research for potential DURC risks, and if applicable, include appropriate risk mitigation measures, such as responsible research communication, in the Category 2 research draft risk mitigation plan.

Table 3 provides examples of risks posed by each type of Category 2 research experimental outcome listed in Section 4.2.2 of the Policy that, when conducted with pathogens described in Section 4.2.1 of the Policy, may be assessed as being reasonably anticipated to result in the development, use, or transfer of a PEPP or an eradicated or extinct PPP that may pose a significant threat to public health, the capacity of health systems to function, or national security. These examples are provided to illustrate the types of risks associated with each experimental outcome and may not represent the full range of possible risks.

Table 3. Examples of Potential Risks Posed by Category 2 Experimental Outcomes

Category 2 Experimental Outcomes	Examples of Associated Risks
i. Enhance transmissibility of the pathogen in humans	• Creates a pathogen more transmissible than the wild-type pathogen such that it is able to spread widely and uncontrollably in the human population. • Creates a pathogen able to survive outside the host and/or withstand environmental conditions longer than the wild-type pathogen, facilitating transmission such that it is able to spread widely and uncontrollably in the human population. • Creates a pathogen with altered tropism (i.e., tissue tropism or host range), that could change the route of transmission, resulting in increased transmissibility relative to the wild-type pathogen such that it is able to spread widely and uncontrollably in the human population. • Increases transmissibility of an animal or zoonotic pathogen, such that it can now utilize new non-human vectors or reservoirs to spread widely and uncontrollably in the human population.
ii. Enhance the virulence of the pathogen in humans	• Creates a pathogen more virulent than the wild-type pathogen (i.e., resulting in higher morbidity or mortality) such that it is able to cause moderate to severe disease in humans.
iii. Enhance the immune evasion of the pathogen in humans such as by modifying the pathogen to disrupt the effectiveness of pre-existing immunity via immunization or natural infection	• Modifies a pathogen such that it is able to spread widely and uncontrollably in the human population, and cause moderate to severe disease, despite existing population immunity against the wild-type pathogen.
iv. Generate, use, reconstitute, or transfer an eradicated or extinct PPP, or a previously identified PEPP	• Reconstitutes or creates a pathogen for which little or no natural immunity exists. • Transfers a reconstructed eradicated or extinct PPP or a previously identified PEPP to another laboratory with or without further experimentation.

B.2.4.1 Pathogens that May be Subject to Category 2 Oversight

Category 2 oversight may be required in three cases:

A) When the starting agent is a PPP **and** the research is reasonably anticipated to result in one of the experimental outcomes to produce a modified pathogen that meets the definition of a PEPP;

B) When the starting agent is a not a PPP **and** the research is reasonably anticipated to result in one of the experimental outcomes to produce a modified pathogen that meets the definition of a PEPP;[9]

C) When one transfers, generates, uses, or reconstitutes an extinct or eradicated PPP, regardless of whether the extinct or eradicated pathogen will be enhanced relative to its wild-type form.

The paragraphs below provide high-level rationale for why certain pathogens are considered PPPs in their wild-type form and others are only considered PPPs after experimental modification. These examples are intended to assist PIs and IREs in their determination of whether their research involves, or is reasonably anticipated to involve, a PPP, and may be reasonably anticipated to result in a PEPP due to expected experimental outcomes. The paragraphs below illustrate some of the considerations that may be taken into account when determining if the pathogen and proposed research should be included in Category 2 research assessment. The rationales in this part of the *Implementation Guidance* are not fully comprehensive but can provide general guidelines for how available quantitative metrics can, on a case-by-case basis, help inform the assessments.

Examples of Pathogens with Pandemic Potential (PPP) in wild-type form

SARS-CoV: SARS-CoV is the etiological agent that causes severe acute respiratory syndrome (SARS). It is an RNA virus transmitted person-to-person most readily through respiratory droplets. During the 2003 outbreak, its basic reproduction rate (R0) was estimated to be about 3 in the absence of controlling measures, giving it potential for wide and uncontrollable spread.[10] However, the lack of transmission before symptom onset allowed for effective implementation of non-pharmaceutical interventions (NPI) to disrupt disease transmission in humans. SARS-CoV is characterized to cause severe disease, given its outbreak case-fatality rate (CFR) was estimated near 10%, with two-thirds of probable cases

[9] The assessment of whether modification of a starting agent that is not a PPP would be reasonably anticipated to result in a PEPP relies on the specific traits of the pathogen and on the type and degree of enhancement being made. For example, enhancing only the virulence of a pathogen that is already highly virulent, but retains limited transmissibility abilities, would not be expected to meet the definition of PEPP and thus not require Category 2 oversight.

[10] Zhang Z. (2007). The outbreak pattern of SARS cases in China as revealed by a mathematical model. Ecological modelling, 204(3), 420–426. https://doi.org/10.1016/j.ecolmodel.2007.01.020.

in the U.S. resulting in hospitalization.[11] While the general population did not have immunity to SARS-CoV,[12] NPIs prevented the 2003 outbreak from reaching pandemic levels. Generally, modifications to SARS-CoV that increase its virulence, transmissibility, or disrupt the effectiveness of pre-existing immunity in humans may be reasonably anticipated to result in a PEPP.

SARS-CoV-2, ancestral lineage, in the absence of population immunity and MCMs: SARS-CoV-2 is the etiological agent that causes coronavirus disease 2019 (COVID-19). It is an RNA virus transmitted person-to-person most readily through respiratory route, with the capability of spreading from infected persons without symptoms. During its emergence in humans in early 2020, the R0 of SARS-CoV-2 was heterogeneous and context dependent, but was greater than 1 and resulted in wide and uncontrollable spread globally. During that time of the pandemic (i.e., January to May 2020), the population had little to no pre-existing immunity and effective countermeasures were not available. The ancestral lineage of SARS-CoV-2 caused moderate to severe disease in individuals at that time: for example, among laboratory-confirmed infections with case reports submitted to CDC between January and May 2020, the case hospitalization rate was estimated at 14% and the CFR at 5.4%.[13] Additionally, pre-symptomatic and asymptomatic transmission dynamics and a range of virulence from asymptomatic to lethal disease contributed to wide and uncontrollable spread on a global level significantly impacting public health, the capacity of health systems to function, and national security. Within the context of early 2020, the ancestral lineage of SARS-CoV-2, or emerging pathogens with comparable characteristics, would be characterized as a PPP due to lack of population immunity and effective medical countermeasures. As of May 2024, SARS-CoV-2 would not be considered a PPP because of the development of vaccines and other effective medial countermeasures, as well as the rise of population immunity. If SARS-CoV-2, regardless of lineage, were genetically modified to enhance transmissibility, virulence, and disrupt effectiveness of pre-existing immunity in humans, it could still be anticipated to result in a PEPP.

Examples of non-PPPs that could result in a PEPP after modification via listed experimental outcome

Ebola virus: Ebola is a term commonly used for disease caused by filoviruses in the genus *Orthoebolavirus*, including most prominently Ebola virus (*Orthoebolavirus zairense*) as well as several other species. These RNA viruses are transmitted person-to-person most readily through direct contact with blood or body fluids from symptomatic infected persons rather than through respiratory route. One review of published estimates proposed a pooled mean R0 for the two most common species of about 2, with high heterogeneity and variability across countries, while acknowledging its R_t can be affected by other characteristics

[11] Update: Severe Acute Respiratory Syndrome --- United States, 2003. MMWR. CDC. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5218a2.htm.

[12] Exposure to other coronaviruses may lead to cross-protective immunity.

[13] Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020. Morbidity and Mortality Weekly Report (MMWR). CDC. https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm.

modifying population susceptibility.[14] Ebola virus causes severe disease. CDC lists outbreaks with estimates of CFR typically greater than 30% and sometimes greater than 80% depending on the outbreak,[15] and essentially all diagnosed illnesses result in hospitalization. Ebola viruses have also caused reoccurring outbreaks since the first recognized cases in 1976, with the largest in 2014-2016 totaling about 28,000 cases and 11,000 deaths. None of these outbreaks progressed to pandemic-level spread, even though specific MCMs were generally not available and resources for implementing NPIs were often limited. Some preventive and therapeutic countermeasures for *Orthoebolavirus zairense* have been approved in recent years that might further help with containment of outbreaks. Based on historical experience with the nature and extent of spread and on the potential for improved control measures, the wild-type Ebola virus is not considered a PPP; however, significant modification to the virus, particularly enhancing transmissibility or disrupting the effectiveness of pre-existing immunity, may result in an Ebolavirus with enhanced pandemic potential, i.e., a PEPP.

SARS-CoV-2, Omicron lineage, given population immunity as of May 2024: SARS-CoV-2 is the etiological agent that causes COVID-19. It is an RNA virus transmitted person-to-person most readily through respiratory route, with the capability of spreading from infected persons without symptoms. The omicron lineage of SARS-CoV-2 became dominant in late 2021 and has spread widely and uncontrollably, with some R0 estimations around 10, but an Rt ranging from 10 to less than 1 depending on levels of pre-existing immunity and other factors.[16] Given population immunity as of May 2024, its CFR is generally considered to be less than 0.5% and it generally is not considered to cause moderate to severe disease in most of the human population.[17] Due to MCMs, including approved vaccines and therapeutics, and the existing population immunity, the circulating omicron lineage of SARS-CoV-2 is currently not considered to pose a significant threat to the capacity for health systems to function or national security. Experiments that are reasonably anticipated to enhance the virulence of or evade pre-existing immunity to the omicron lineage SARS-CoV-2, or other emerging variants with similar characteristics, may result in a PEPP.

Highly Pathogenic Avian Influenza A(H5) and A(H7) subtypes: Avian influenza A viruses may cause severe (highly pathogenic avian influenza, HPAI) or mild/inapparent (low pathogenic avian influenza, LPAI) infections in poultry, can infect and be transmitted by wild birds, and occasionally spill over to sporadic mammalian, including human, infections. Either HPAI or LPAI can cause either mild or severe infections in humans. Particular concern has been raised regarding the potential for severe and fatal human infections with H7N9 and H5N1, with estimated CFRs of about 40-50% of detected cases, although the completeness of

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[14] Basilua Andre Muzembo, Kei Kitahara, Debmalya Mitra, Ngangu Patrick Ntontolo, Nlandu Roger Ngatu, Ayumu Ohno, Januka Khatiwada, Shanta Dutta, Shin-Ichi Miyoshi, The basic reproduction number (R0) of ebola virus disease: A systematic review and meta-analysis, Travel Medicine and Infectious Disease, Volume 57, 2024, 102685, ISSN 1477-8939, https://doi.org/10.1016/j.tmaid.2023.102685

[15] History of Ebola Outbreaks. CDC. https://www.cdc.gov/vhf/ebola/history/chronology.html.

[16] Liu, Y., & Rocklöv, J. (2022). The effective reproductive number of the Omicron variant of SARS-CoV-2 is several times relative to Delta. Journal of travel medicine, 29(3), taac037. https://doi.org/10.1093/jtm/taac037.

[17] Horita, N., & Fukumoto, T. (2023). Global case fatality rate from COVID-19 has decreased by 96.8% during 2.5 years of the pandemic. Journal of medical virology, 95(1), e28231. https://doi.org/10.1002/jmv.28231.

detection is unclear and milder cases have also been reported. However, human-to-human transmission has been rare and non-sustained. There are several MCMs or candidate MCMs that might also help to limit transmission depending on specific circumstances. Because A(H5) and A(H7) viruses do not transmit efficiently in humans, they are not considered PPPs in their wild-type state.[18] However, because they can cause moderate to severe disease in humans, modification of A(H5) and A(H7) viruses that facilitate enhanced human-to-human transmission compared to their parental strains could reasonably be anticipated to pose a significant threat to public health, the capacity of health systems to function, or national security, and result in a PEPP. This type of research would be considered Category 2 and necessitate department-level review before the research commences or proceeds.

Note: Research that is reasonably anticipated to result in one or more of the experimental outcomes listed in Section 4.1.2 of the Policy on an HPAI virus such as A(H5) or A(H7), if not designated as Category 2 research, may be considered Category 1 research due to the viruses' potential to pose a significant threat to animals.

B.2.4.2 Experiments that May be Subject to Category 2 Oversight

Examples of experiments that could be reasonably anticipated to result in creation of a PEPP, include but are not limited to:

- Certain serial passaging experiments to select for increased virulence and/or transmissibility in animal models and/or cell and organoid systems that are designed to model human pathogenesis or transmission[19]
    a. Examples of serial passaging experiments that could fall under Category 2 oversight include:
        i. Serial passaging a respiratory pathogen that replicates in ferrets to select for increased transmissibility between animals, as ferrets have a similar lower and upper respiratory tract as humans and are often used as human surrogates for transmission studies.
        ii. Serial passaging experiments in primary human cells or human organoid systems that are reasonably anticipated to select for increased virulence or transmissibility in humans.
    b. Examples of serial passaging experiments that are not included in Category 2 oversight:

[18] Should any variant HPAI A virus emerge that similarly causes moderate to high disease in humans and gains efficient human-to-human transmission with potential for wide and uncontrollable spread, these emergent wild-type viruses would be considered PPPs; and in many cases, modification that is reasonably anticipated to, or does, enhance transmission, virulence, or immune evasion would make resulting product a PEPP and be considered Category 2 research.

[19] Note: Not all human transgenic animal models or species used for animal models are designed to accurately model the complexity of human pathogenesis. Similarly, not all human transgenic animal models or species used for animal models are necessarily appropriate surrogates for studying transmissibility in humans.

i. A mouse model designed to overexpress a human receptor to study viral infection that result in abnormal pathogenesis (e.g., encephalitis). Increased virulence in the mouse model does not necessarily represent increased virulence in humans due to differences in receptor expression compared to humans.
ii. Serial passaging in animal models to adapt the virus to that system in order to develop a model for pathogenesis often results in mutations that improve replication for that species and diverge away from infecting humans.

- Experiments deliberately generating PPP strains that are resistant to FDA-approved, cleared, or licensed MCMs, when such resistance trait(s) are not known to occur naturally and such resistance trait(s) could compromise the ability to control the morbidity, mortality, or spread in humans.
- Modifying the host range of highly virulent animal pathogens (e.g., avian influenza) to increase transmission between humans or animal reservoirs and humans.
- Creating a chimera from two PPPs such that the resulting pathogen could have enhanced transmission or virulence as compared to at least one of the progenitor pathogens.
- Assembling and rescuing infectious 1918 pandemic influenza virus through a reverse genetics protocol.

B.2.4.3 Experiments that are Not Typically Subject to Category 2 Oversight

The following types of experiments are not typically within scope of Category 2 research because the outcomes or actions typically do not result in the enhancement of a pathogen's transmissibility or virulence or a disruption of the effectiveness of pre-existing immunity resulting in a PEPP as outlined in Section 4.2. However, PIs are expected to exhibit vigilance and evaluate research in case unexpected results warrant Category 2 review for the development, use, or transfer of a PEPP.

Note: Category 1 Research oversight may apply if the agent is on the Category 1 list and genetic manipulation or laboratory adaptation is reasonably anticipated to result in one of the experimental outcomes listed in Section 4.1.2 of the Policy in a manner that would constitute DURC. These protocols should be evaluated for Category 1 designation by the PI and IRE and a risk mitigation plan should be developed, as appropriate.

- Surveillance activities, including collection of diagnostic and clinical specimens, sampling and sequencing, and basic viral characterization, in which the pathogen or toxin is not modified via genetic manipulation or laboratory adaptation to enhance transmissibility or virulence in humans such that it can spread uncontrollably in human population and cause moderate to severe disease.

- Research on evaluating, testing, and/or producing vaccines and related biologics such as immunoglobulins and the generation of high-growth strains, with the attenuation of virulence and transmissibility below wild-type levels.

- Experiments focused on evaluating and developing antivirals for the treatment or prevention of disease caused by circulating human viruses, when generation of antiviral resistant strains are not reasonably anticipated to result in a PEPP.

- Basic viral characterization studies, including but not limited to, pseudotype virus studies with proteins from laboratory-adapted strains, human receptor binding studies, animal model susceptibility studies that do not involve serial transmission, and *in vitro* experiments with human cell lines or primary human cells that do not involve certain types of serial passage that would be considered higher risk.

For further examples on how to identify and assess Category 2 research, refer to Appendix D of this *Implementation Guidance* for illustrative scenarios.

B.3 Explanation of Reasonably Anticipated

As described in the Policy, the phrase "reasonably anticipated" describes "an assessment of an outcome such that, generally, individuals with scientific expertise relevant to the research in question would expect this outcome to occur with a non-trivial likelihood. It does not require high confidence that the outcome will definitely occur and excludes experiments in which experts would anticipate the outcome to be technically possible, but highly unlikely."

This definition is meant to capture several important features of the assessment:

"Generally, individuals with scientific expertise relevant to the research in question": Relevant scientific expertise is required to anticipate the potential and plausible results of an experiment. Scientists may have differing views on possible and likely outcomes of any particular experiment, so the general assessment of multiple individuals is likely to be more robust than the views of any single individual. The PI is not required to seek assessment from a group of individuals, but rather to use the PI's individual expertise and experience to consider the range of assessments that individuals with relevant scientific expertise would likely make.

"Expect this outcome to occur": While it is impossible to know for certain the result of any experiment in advance, experiments are typically conducted to test specific hypotheses. These hypotheses constitute expectations about the possible results of an experiment, and should be included in the range of results that are "reasonably anticipated" may occur. The PI may consider, if applicable, leveraging existing literature that may have analogous experimental design and/or similar pathogens or toxins to determine potential expectations.

"Non-trivial likelihood": A "reasonably anticipated" outcome is not necessarily the most likely outcome, nor is it necessarily an outcome with greater than 50% likelihood. Rather, it is an outcome that has a reasonable, non-negligible chance of occurring. For example, consider an experiment on pandemic influenza that experts anticipate is most likely to result in a loss

of function, but that experts also believe could possibly increase transmissibility of the pathogen. An indication of generating a pandemic influenza virus with enhanced transmissibility represents a risk of high consequence to the public if that agent were to be accidentally released. Such a study should therefore undergo Category 2 oversight because, despite the fact that generating a PEPP is not the likeliest outcome, it has a non-trivial likelihood of resulting in a PEPP.

"Excludes experiments in which an expert would anticipate the outcome to be technically possible, but highly unlikely": For many experiments it may be possible to imagine a scenario, however unlikely, in which a genetic mutation surprisingly results in an increase in virulence or transmissibility against all reasonable expectations and prior evidence. The purpose of the Policy is to prioritize oversight for experiments that may pose the greatest risks. Technically plausible outcomes with very low likelihoods, as assessed based on pre-existing evidence, are not subject to Category 2 oversight. As per the Policy, if such a result unexpectedly arises during the conduct of research, the study should be halted, immediately be flagged for the IRE and funding entity, and be subject to Category 2 assessment and risk mitigation.

C. GENERAL OVERVIEW OF THE POLICY OVERSIGHT FRAMEWORK

This part of the *Implementation Guidance* describes the organizational framework for research oversight and broadly articulates the roles and responsibilities of entities that conduct research (i.e., PIs and research institutions) and entities that fund or sponsor research (i.e., federal funding agencies). The framework will be implemented by federal funding agencies in compliance with applicable laws, regulations, and policies, such as through the development of terms and conditions for funding awards. See **Figure 1** for a graphic representation of the workflow. Generally, the process for the research oversight system described in the Policy is as follows:

1. The PI makes an initial assessment of whether their proposed or ongoing research may be within scope of Category 1 and/or Category 2 based upon i) the biological agent or toxin and ii) the experimental outcome or actions (as specified in the Policy in Section 4.1.1 and Section 4.1.2 for Category 1 research, and Section 4.2.1 and Section 4.2.2 for Category 2 research).

   PIs and IREs are reminded to also assess Category 2 research for potential DURC risks. The research institution is responsible for ensuring that PIs are aware of and executing this responsibility appropriately.[20]

2. The PI submits the research proposal to the federal funding agency and includes a

[20] As indicated in Section 5.3.G of the Policy, if a research institution outside of the United States is unable to meet one or more of the criteria in Section 5.2.B of the Policy but the federal funding agency nevertheless determines that it remains in the best scientific interest to fund the research, the federal funding agency will serve as the implementing IRE or take other steps it determines are needed to ensure adequate biosafety and biosecurity oversight of Category 1 and Category 2 research.

notification that the research may be within scope of Category 1 and/or Category 2 based on the biological agent or toxin and the experiment.

3. When the federal funding agency has completed merit review of the proposed research and if it is considering funding the proposed research, the federal funding agency notifies the research institution.

4. The research institution, through an IRE, reviews the PI's initial assessment and confirms whether proposed or ongoing research is within the scope of Category 1 and/or Category 2 research. If so, the IRE determines whether the research is Category 1 or Category 2, based on a risk assessment under Section 4.1.3 (for Category 1) or Section 4.2.3 (for Category 2) of the Policy. The research institution notifies the federal funding agency of the results of its determination, and the federal funding agency evaluates and verifies the research institution's assessment. Examples of risk assessment measures are described in Part E of this *Implementation Guidance*.

   Note: Any research that meets the definition of both Category 1 and Category 2 research is designated as Category 2 research and must proceed through Category 2 assessment and risk mitigation.

5. If the research is assessed to be Category 1 or Category 2, the research institution, through an IRE, should conduct risk-benefit assessments and develop a draft risk mitigation plan for the conduct and communication of the research. The PI or research institution submits the risk-benefit assessments and a risk mitigation plan to the federal funding agency. Examples of risk mitigation approaches are described in Part F in this *Implementation Guidance*.

6. The federal funding agency reviews the risk-benefit assessments and risk mitigation plan as follows:
   - For specific experiments within the research proposal determined to be Category 1, the federal funding agency evaluates the research institution's risk-benefit assessments and determines whether the potential benefits justify the potential risks prior to the funding decision. These specific experiments will not proceed until the federal funding agency approves the risk mitigation plan.

   - For specific experiments within the research proposal determined to be Category 2, the federal funding agency refers the proposed research for department-level review.[21] Upon receipt of the Category 2 research proposal, the department convenes a multidisciplinary review entity to evaluate the research institution's risk-benefit assessments and risk mitigation plan prior

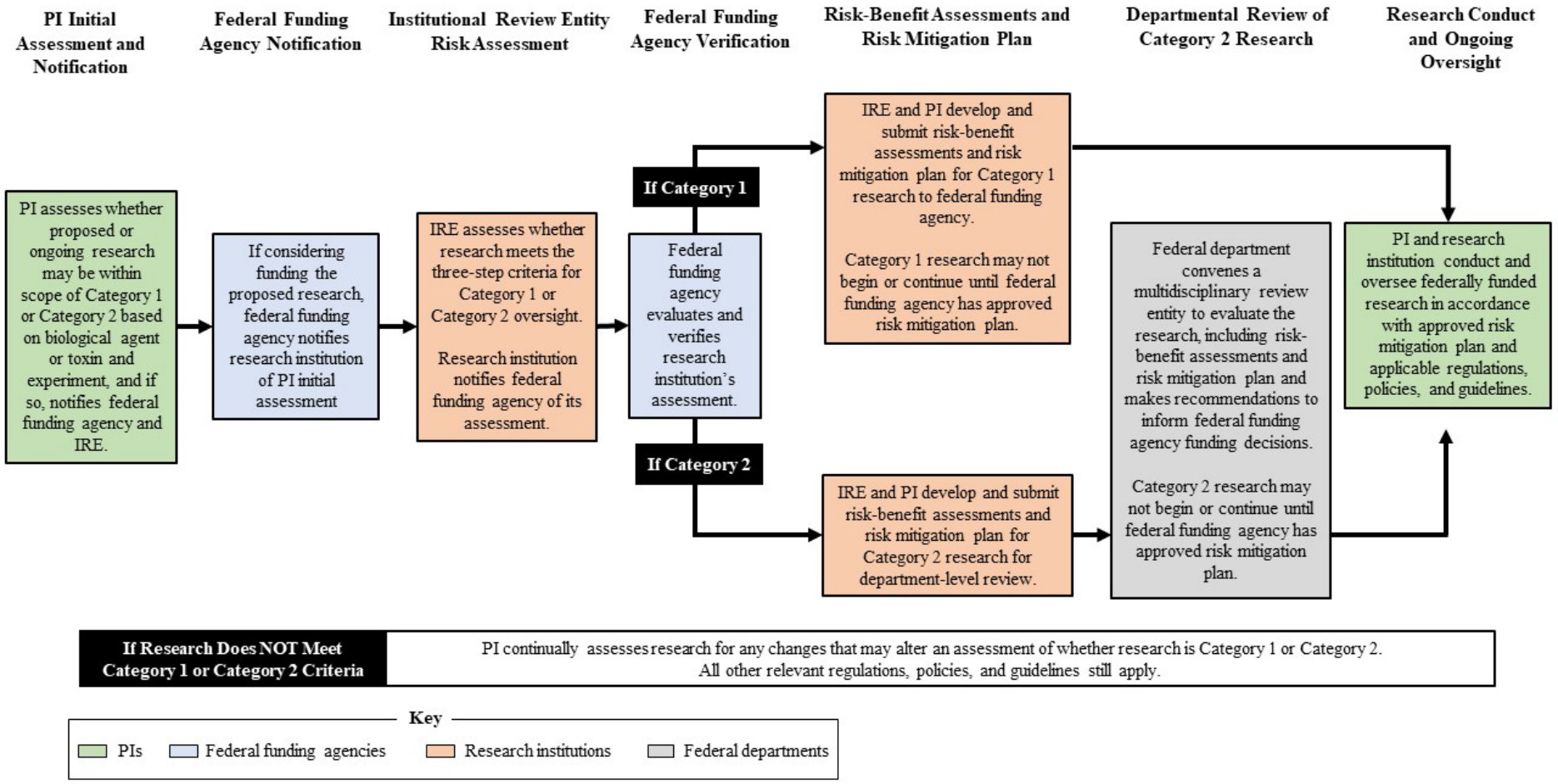
[21] In some cases, the federal funding agency and the department funding an in-scope research study are distinct (e.g., National Institutes of Health and the Department of Health and Human Services) and in other cases they are the same (e.g., National Science Foundation). Federal departments and agencies will implement the Policy based on their specific structure.

to the federal funding agency making a funding decision on the research proposal. The multidisciplinary review entity will make recommendations to the federal funding agency regarding the risk-benefit assessments, risk mitigation plan, and research proposal funding. The specific experiments within the research proposal determined to be Category 2 will not proceed until the federal funding agency determines that the potential benefits justify the potential risks and approves the risk mitigation plan.

7. If research is identified as potentially within the scope of Category 1 or Category 2 research during the course of experimentation, the PI should halt further work, notify the federal funding agency, and contact their IRE to conduct the required assessments consistent with the procedures in the Policy for assessing Category 1 or Category 2 research.

It is the responsibility of PIs and research institutions to identify research that may fall within scope of Category 1 and/or Category 2 research. Federal funding agencies have the discretion to request additional information or review of individual research proposals or projects to determine whether they may fall within scope of Category 1 or Category 2 research. PIs should also provide annual progress reports for Category 1 research and semiannual progress reports for Category 2 research, and as requested by the federal funding agency (e.g., as part of terms and conditions of award or risk mitigation plans), for review, evaluation, assessment, and, where necessary, clarification or confirmation

Figure 1. Overview of Review Process for Category 1 or Category 2 Research. Depicts the general workflow for review and assessment of research under to the Policy involving PIs (green boxes), research institutions (peach boxes), federal funding agencies (blue boxes), and federal departments (gray box).



D. GUIDANCE FOR PRINCIPAL INVESTIGATORS: ASSESSMENT FOR POTENTIAL CATEGORY 1 AND CATEGORY 2 RESEARCH AND OTHER RESPONSIBILITIES

A summary of key actions and responsibilities for PIs during the review and assessment of research are provided below. As a reminder, the PI is not required to definitively determine whether their research is Category 1 or Category 2, but rather to identify whether their research is, or is reasonably anticipated to, involve a biological agent described in Section 4.1.1 or Section 4.2.1 of the Policy, and whether their research is reasonably anticipated to result in one or more of the research experimental outcomes listed in Sections 4.1.2 or 4.2.2 of the Policy, respectively. Upon notification to the funding agency and institution, the IRE assesses whether the research meets the thresholds to be designated Category 1 or Category 2 research outlined in Section 4.1.3 and/or Section 4.2.3 of the Policy (see Part E of this *Implementation Guidance* for IRE responsibilities).

PIs should assess their research at the proposal stage and continuously throughout the entire course of research for its potential to be within scope of Category 1 or Category 2 research. It is recommended PIs begin their processes by considering whether their research may be within scope of Category 2 first, and then considering Category 1 as described below in D.1 and D.2, respectively.

These key actions and responsibilities are not necessarily recommended to be implemented sequentially 1 through 8. Depending on the outcome at key steps, indicators in the details below can help guide workflow order. See **Figure 2** for a graphic representation of the PI's workflow.

Note: Any research that meets the definition of both Category 1 and Category 2 research is designated as Category 2 research and must proceed through Category 2 assessment and risk mitigation.

D.1 Assess for Potential to be in Scope of Category 2 Research

Step 1: Assess whether research involves, or is reasonably anticipated to result in, a PPP.

PIs should assess their research at the proposal stage and continuously throughout the research lifecycle to identify whether research is reasonably anticipated to be within scope of Category 2. PIs should identify whether a PPP will be involved at any point of the research lifecycle, regardless of its progenitor agent. In many cases, this includes consideration of the characteristics of the starting agent as well as those of the pathogen(s) anticipated to result from the proposed experiments. If an experimental outcome results in a non-PPP meeting the definition of a PPP, then the research is in scope of Category 2. A PPP is defined as "a pathogen that is likely capable of wide and uncontrollable spread in a human population and would likely cause moderate to severe disease and/or mortality in humans." More information on defining PPP can be found in Part B.2.1 of this *Implementation Guidance*. Extinct or eradicated PPPs should be considered as well.

- If the research involves a PPP or is reasonably anticipated to result in a PPP, including the generation, use, reconstitution, or transfer of an eradicated, extinct, or existing PPP, proceed to **Step 2**.

- If the research is NOT found to involve a PPP, is not reasonably anticipated to result in a PPP, including generation, use, reconstitution, or transfer an eradicated, extinct, or existing PPP, proceed to **Step 3**.

Step 2: Assess whether research is reasonably anticipated to result in, or does result in, one or more of the listed experimental outcomes or actions in scope of Category 2 research.

The four experimental outcomes or actions listed in Section 4.2.2 of the Policy include three that directly affect pathogen characteristics. To assess whether their research is reasonably anticipated to result in, or does result in, one or more of the listed experimental outcomes or actions, the PI should consider the hypothesis being tested and the likelihood that the experiments will enhance the transmissibility, virulence, and/or immune evasion of the pathogen in humans. The PI should additionally consider whether the research involves transferring or using an eradicated or extinct PPP or a previously identified PEPP, regardless of whether the research is expected to modify the pathogen. Table 3 provides illustrative examples of risks associated with the listed experimental outcomes on pathogens identified in Step 1. Part B.2.4.2 and Part B.2.4.3 of this *Implementation Guidance* provide examples of experiments that may or may not be subject to Category 2 oversight.

- If the research is reasonably anticipated to result in, or does result in, one or more of the listed experimental outcomes or actions as described in Section 4.2.2 of the Policy, proceed to **Step 5**.

- If the research is NOT reasonably anticipated to result in one or more of the listed experimental outcomes or actions as described in Section 4.2.2 of the Policy, proceed to **Step 3**.

D.2 Assess for Potential to be in Scope of Category 1 Research

Step 3: Assess whether research involves one or more of the listed biological agents or toxins.

PIs should assess their research at the proposal stage and continuously throughout the research lifecycle to identify whether their research directly involves one or more of the biological agents or toxins described in Section 4.1.1 of the Policy. A checklist of these biological agents and toxins is included in Appendix C of this *Implementation Guidance*.

- If the research involves one or more of the biological agents or toxins listed in Section 4.1.1 of the Policy, the PI should proceed to **Step 4**.

- If the research does NOT involve one or more of the biological agents listed in Section 4.1.1 of the Policy, PIs do not need to notify the funding agency or their IRE, and their research is not subject to additional oversight under this Policy. If at any time their

research is reasonably anticipated to result, or does result, in one or more of the listed experimental outcomes on a designated biological agent or toxin identified in Steps 1 through 3, the PI should will halt further work, notify the federal funding agency, and refer the research to the IRE for further Category 1 or Category 2 review.

Step 4: Assess whether research is reasonably anticipated to result, or does result, in one or more of the listed experimental outcomes in scope of Category 1 research.

To assess whether their research is reasonably anticipated to result in, or does result in, one or more of the experimental outcomes listed in Section 4.1.2 of the Policy, the PI should consider the hypothesis being tested and likelihood of any of the outcomes resulting from the experiments to be conducted. Table 2 provides illustrative examples of risks associated with Category 1 experimental outcomes in scope of Category 1 research.

- If the research is reasonably anticipated to result, or does result, in one or more of the listed experimental outcomes on a designated biological agent or toxin, proceed to **Step 5**.

- If the research does NOT involve one or more of the listed experimental outcomes, PIs do not need to notify the funding agency or their IRE, and their research is not subject to additional oversight under this Policy. If at any time their research is reasonably anticipated to result, or does result, in one or more of the listed experimental outcomes on a designated biological agent or toxin identified in Steps 1 through 3, the PI should halt further work, notify the federal funding agency, and refer the research to the IRE for further Category 1 or Category 2 review.

D.3 Risk-Benefit Assessments, Risk Mitigation Plan, and Conduct and Oversight of Category 1 or Category 2 Research

Step 5: Notify funding agency and refer research to IRE.

PIs should notify the federal funding agency and refer to the IRE research assessed as being within scope of Category 1 (i.e., (1) it involves one or more of the listed biological agents or toxins described in Section 4.1.1 of the Policy AND (2) is reasonably anticipated to result in one or more of the Category 1 experimental outcomes described in Section 4.1.2 in the Policy) and/or Category 2 (i.e., (1) it involves, or is reasonably anticipated to result in, a PPP including the generation, use, reconstitution, or transfer of an eradicated, extinct, or existing PPP described in Section 4.2.1 of the Policy AND (2) is reasonably anticipated to result in one or more of the Category 2 experimental outcomes or actions described in Section 4.2.2 of the Policy). PIs are encouraged to consult with relevant funding agency and institutional officials regarding the appropriate process for such notifications and referrals.

A PI's assessment that their research is within scope of Category 1 or Category 2 does not necessarily mean the research is subject to Category 1 or Category 2 research oversight. It is the responsibility of the IRE to assess research referred by the PI to determine whether it meets the threshold to be designated as Category 1 or Category 2 research. The federal funding agency is responsible for evaluating and verifying the IRE's assessment.

If the federal funding agency is considering funding, the PI should be aware that further assessment of their research is required before funding can begin or research can continue.

Step 6: Work with IRE to assess risks and benefits and draft risk mitigation plan.

PIs should work with the IRE to assess the risks and benefits of Category 1 or Category 2 research and submit risk-benefit assessments and a draft risk mitigation plan to the federal funding agency considering funding the research for review and approval when appropriate.

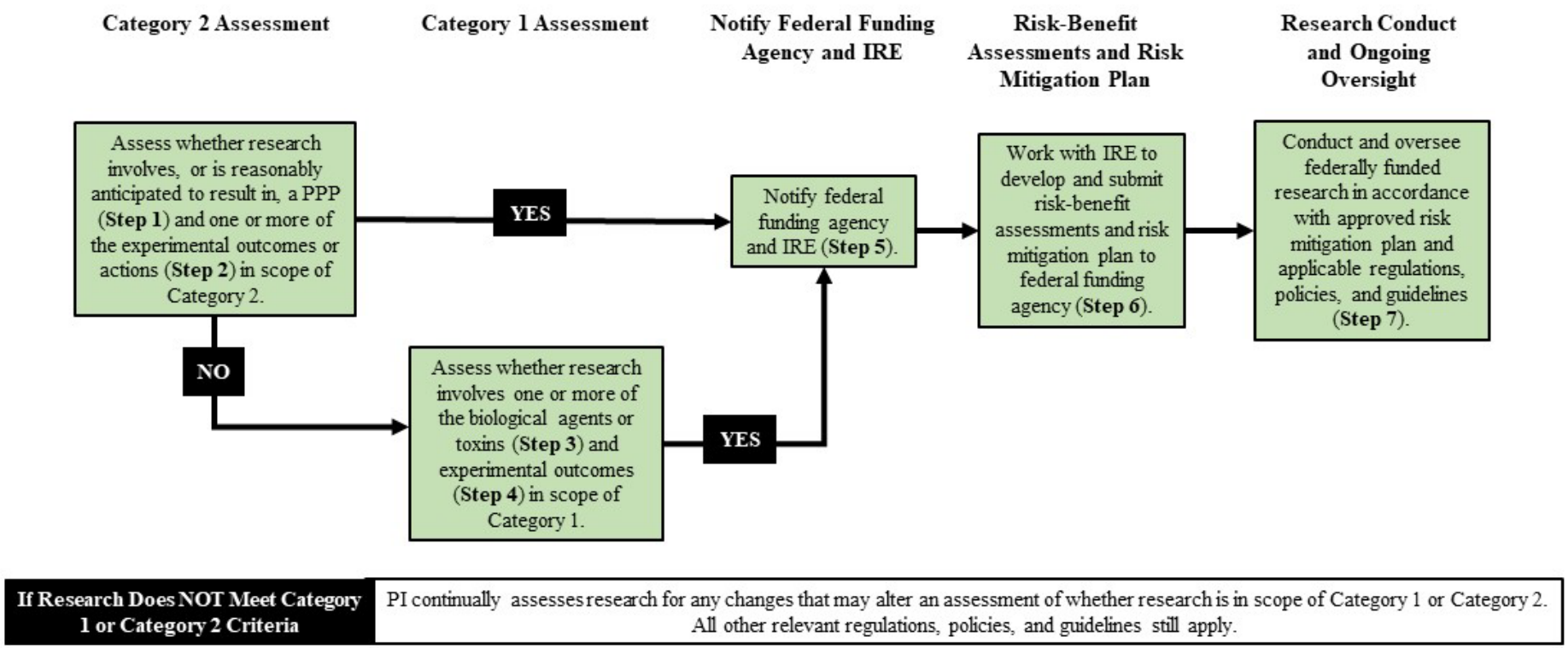
Step 7: Conduct and communicate research responsibly

PIs are responsible for carrying out research in accordance with the provisions identified in the risk mitigation plan approved by the federal funding agency. PIs are also responsible for ensuring that laboratory personnel conducting life sciences research within the scope of this Policy (i.e., those under the supervision of laboratory leadership including graduate students, postdoctoral fellows, research technicians, laboratory staff, and visiting scientists) have received and maintain education and training on all research oversight policies and processes and demonstrate competency.

PIs should also provide annual progress reports for Category 1 research and semiannual progress reports for Category 2 research, and as requested by the federal funding agency (e.g., as part of terms and conditions of award or risk mitigation plans), for review, evaluation, assessment, and, where necessary, clarification or confirmation.

PIs should communicate Category 1 and Category 2 research in a responsible manner. Communication of research and research findings is an essential activity for all researchers that occurs throughout the research process, not only at the point of publication. When researchers are planning to communicate Category 1 and Category 2 research results, it is their duty to ensure that it is done in a responsible manner and follows any risk mitigation plan approved by the federal funding agency.

Figure 2. PI Review Process for Category 1 or Category 2 Research. Depicts the PI workflow for review and assessment of research that might be subject to the Policy.



E. GUIDANCE FOR INSTITUTIONAL REVIEW ENTITIES: REVIEW PROCESS FOR CATEGORY 1 AND CATEGORY 2 RESEARCH

A summary of the key actions and responsibilities for IREs during the review and assessment of research is provided below. As a reminder, the IRE is not required to review the research for Category 1 or Category 2 designation until after the federal funding agency has determined that the research is eligible for federal funding based on a scientific merit review. It is recommended that IREs begin their processes by considering whether the proposed studies fall under Category 2 research first, and then considering Category 1 research as described below in E.1 and E.2, respectively. These key actions and responsibilities are not necessarily recommended to be implemented sequentially 1 through 11. Depending on the outcome at key steps, indicators in the details below can help guide workflow order. See **Figure 3** for a graphic representation of the workflow.

Note: Any research that meets the definition of both Category 1 and Category 2 research is designated as Category 2 research and must proceed through Category 2 assessment and risk mitigation.

E.1 Assess for Category 2 Research

Step 1: Confirm that the research involves, or is reasonably anticipated to result, in, a PPP.

To determine whether research should be designated as Category 2, the IRE should assess and confirm the PI's assessment that the research involves, or is reasonably anticipated to result in, a PPP, as specified in 4.2.1 of the Policy. More information on how to assess this is included in Part B.2 of this *Implementation Guidance*.

- If the research involves a PPP or is reasonably anticipated to result in a PPP, including the generation, use, reconstitution, or transfer of an eradicated, extinct, or existing PPP, proceed to **Step 2**.
- If the research is NOT found to involve a PPP and is NOT reasonably anticipated to result in a PPP, including generation, use, reconstitution, or transfer an eradicated, extinct, or existing PPP, proceed to **Step 4**.

Step 2: Confirm that the research is reasonably anticipated to result in, or does result in, one or more of a listed experimental outcomes or actions in scope of Category 2 research.

To determine whether research should be designated as Category 2, the IRE should assess and confirm the PI's assessment that the research is reasonably anticipated to result in, or does result in, one or more of a listed experimental outcomes or actions, listed in Section 4.2.2 of the Policy.

- If the research is reasonably anticipated to result in, or does result in, one or more of the listed experimental outcomes or actions as described in Section 4.2.2 of the Policy, proceed to **Step 3**.

- If the research is NOT reasonably anticipated to result in one or more of the listed experimental outcomes or actions as described in Section 4.2.2 of the Policy, proceed to **Step 4**.

Step 3: Assess risks of potential Category 2 research and determine whether research should be designated as Category 2.

To determine if research should be designated as Category 2, the IRE should assess the research for biosafety and biosecurity risks. In performing the risk assessment, the IRE should examine descriptions of the research in question, the PI's assessment of the applicability of the pathogen (Step 1) and categories of experimental outcome or action (Step 2), and other relevant information. In designating research as Category 2, the IRE is required to determine whether the research can be reasonably anticipated to result in the development, use, or transfer of a PEPP, or an eradicated or extinct PPP that may pose a significant threat to public health, the capacity of health systems to function, or national security, as outlined in Section 4.2.3 of the Policy.

Key to this Category 2 determination is an assessment of whether the research involves a pathogen that, through one or more of the listed experimental outcomes, *may pose a significant threat to public health, the capacity of health systems to function, or national security*. Research involving PPPs, whether eradicated, extinct, or existing, may not always rise to the level of posing this type of significant threat as indicated above. In such cases, the research would not be considered to reasonably result in the development, use, or transfer of a PEPP or extinct or eradicated PPP needing Category 2 oversight. Factors that could be useful in determining these types of significant threats include the pathogen's cumulative capability for wide and uncontrollable spread, extent of disease, the degree of pre-existing population immunity, and the availability of MCMs to provide preventative and treatment interventions, and other public health and social considerations. For example, if upon exposure or misuse of the pathogen the nation's hospital systems were to become inundated with patients infected with a pathogen causing moderate to severe disease morbidity and/or mortality, it would pose a significant threat to public health, the capacity of health systems to function, or national security. More information on how to assess this is included in Section B.2 of this *Implementation Guidance*.

Examples of materials to consider during this risk assessment include the project proposal, any project reports, and examples of similar research in the literature. Biosafety and biosecurity assessments should also identify hazardous potential of the pathogen or information as a result of identified experimental outcome(s), actions that can reasonably result in exposure to or misuse of the potential PEPP or information, likelihood that such exposure or misuse will occur, and potential consequences of such an exposure or misuse. Established risk assessment models such as those described in the Biosafety in Microbiological Biomedical Laboratories (BMBL) or *NIH Guidelines* can help guide these assessments. IREs are encouraged to consult with their relevant institutional, local, or state

security offices and departments, as appropriate, for any additional factors that may be helpful to consider when conducting assessments related to public health, the capacity of health care systems to function, or of a significant threat to national security.

There are two potential outcomes following the risk assessment:

- If the research can be reasonably anticipated to result in the development, use, or transfer of a PEPP or an eradicated or extinct PPP that poses a significant threat to public health, the capacity of health systems to function, or national security, designate the research as Category 2 research. The IRE should proceed to **Step 6a** to assess the Category 2 research for potential DURC risks, and then notify the funding agency of the Category 2 designation (**Step 7**).

- If the research is NOT reasonably anticipated to result in the development, use, or transfer of a PEPP or an eradicated or extinct PPP that poses a significant threat to public health, the capacity of health systems to function, or national security, the research does not meet the scope of Category 2 research and the IRE does not need to proceed with Category 2 assessment and risk mitigation. The IRE should proceed to **Step 4** to evaluate the research for Category 1 designation. However, the PI should be informed that if at any time the reviewed research may meet the scope of Category 1 or Category 2 research, the PI should halt further work, refer the research again to the IRE for review, and notify the funding agency.

E.2 Assess for Category 1 Research

Step 4: Confirm that the research involves one or more of the listed biological agents or toxins.

To determine whether research should be designated as Category 1, the IRE should assess and confirm that the PI's assessment that the research directly involves one or more of the biological agents or toxins listed described in Section 4.1.1 of the Policy. A checklist of these biological agents and toxins is included in Appendix C of this *Implementation Guidance*.

- If the research involves one or more of the biological agents or toxins listed in Section 4.1.1 of the Policy, the IRE should proceed to **Step 5**.

- If the research does NOT involve one or more of the biological agents listed in Section 4.1.1 of the Policy, the research should not be designated as Category 1 research and the IRE does not need to continue with the Category 1 assessment and risk mitigation. However, the IRE must still proceed to **Step 7** to notify the appropriate federal funding agency of its findings. The PI should be informed that if at any time the reviewed research may meet the definition of Category 1 or Category 2 research, the PI should halt further work, refer the research again to the IRE for review, and notify the federal funding agency.

Step 5: Confirm that the research is reasonably anticipated to result, or does result, in one or more of the listed experimental outcomes in scope of Category 1 research.

To determine whether research should be designated as Category 1, the IREs should assess and verify the PI's assessment of whether the research is reasonably anticipated to result, or does result, in one or more of the listed experimental outcomes listed in Section 4.1.2 of the Policy.

The IRE should examine descriptions of the research in question, the PI's assessment of the applicability of the categories of experiments, and other relevant information, as warranted. Examples of materials to consider include the project proposal, any project reports, any previous outcomes of dual use reviews, and examples of similar research in the literature.

- If the research is reasonably anticipated to result, or does result, in one or more of the listed experimental outcomes on a designated biological agent or toxin identified in Step 4, proceed to **Step 6** to assess dual use risks and determine whether the research should be designated as Category 1 research.

- If NONE of the listed experimental outcomes applies, the research should not be designated as Category 1 research and the IRE does not need to continue with the Category 1 assessment and risk mitigation. However, the IRE must proceed to **Step 7** to notify the appropriate federal funding agency of its findings. The PI should be informed that if at any time in the future if the reviewed research may meet the definition of Category 1 or Category 2 research, the PI should halt further work, and refers the research again to the IRE for review, and notify the federal funding agency.

Step 6: Assess the dual use risk associated with the research and determine whether research should be designated Category 1 (if applicable).

Step 6a: Assess the dual use risk associated with the research.

Research already designated as Category 2, or research being assessed as potential Category 1, should next be assessed for risks associated with DURC.

DURC is defined in Section 3 of the Policy as "life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be misapplied to do harm with no, or only minor, modification to pose a significant threat with potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security."

When considering whether the research in question meets the definition of DURC, the IRE should identify the risks associated with the potential misuse of the information, technologies, or products that may be generated. Although risk assessments may be either quantitative or qualitative, the assessment process outlined below is qualitative in nature and requires the consideration and judgment of the IRE on the following:

A) The ways in which knowledge, information, technologies, or products from the research could be misused to harm public health and safety, agriculture, plants, animals, the environment, materiel, or national security.

B) The ease with which the knowledge, information, technologies, or products might be misused and the feasibility of such misuse.

C) The magnitude, nature, and scope of the potential consequences of misuse.

The IRE should consider the points in **Box 1** below to assess the potential risks associated with conducting the research in question or communicating its results at any time during the lifecycle of the project. These points address some of the aspects of potential DURC that could be considered, but they are not exhaustive –— IREs should augment these points to fit their needs and the research under consideration. This risk assessment is intended to assist IREs in determining whether the research in question meets the definition of DURC. In cases where the research is determined to be DURC, this assessment will also inform the subsequent process of identifying strategies for mitigating those risks.

Box 1: Points to Consider in Assessing Research for its Dual Use Potential

- **Type of Misuse**: In what ways could the knowledge, information, products, or technologies from the research be misused? The risk of misuse may be higher for research that can be directly misused than for research that requires significant additional scientific advances to facilitate its misapplication.
    - What types of knowledge, information, products, or technologies are anticipated to be generated through the research?
    - Can the knowledge, information, products, or technologies from the research be misapplied with no, or only minor, modification to cause harm?
        - If so, how?
        - If not, do the outcomes of the research need to be combined with other knowledge, information, products, or technologies in order to pose a threat? If so, is the other knowledge, information, products, or technologies already or readily available?
    - Is there concern about immediate or near-future potential misuse, or is the concern about misuse in the distant future? Consider the time frame in which information from the research might be misused. Information that can be misused in the near term may be of greater concern.
- **Ease of Misuse**: How easily could the knowledge, information, products, or technologies be misapplied to do harm with no, or only minor, modification? Consider the technical expertise and/or physical resources that would be required to apply the knowledge, information, products, or technologies for malevolent purposes. The risk of

misuse may be lower for knowledge, information, products, or technologies that would be expensive, difficult to procure, or that require a high degree of technical skill to facilitate such misuse.

  - Would misuse of the knowledge, information, products, or technologies require a low or high degree of technical skill and sophistication to use the information from dual use research for harmful purposes? Alternatively, would it make achieving the harmful outcome easier for an unsophisticated actor?

  - Would misuse of the knowledge, information, products, or technologies require materials, equipment, or reagents that are expensive or difficult to procure?

- **Dissemination**: How will the knowledge, information, products, or technologies of the research in question be shared or distributed? Knowledge, information, products, or technologies that are freely available and widely distributed may be more easily accessed by individuals with harmful intent.

  - Who will have access to the knowledge, information, products, or technologies?

  - Will the knowledge, information, products, or technologies be shared openly or remain within the laboratory?

- **Information Risks**: What is the novelty of the information provided by the research or research methods? Research that adds novel information or consolidates information in novel ways may be of greater concern than information that is already widely available.

  - Have the results of similar research been previously described or shared? If so, at what venues and in what detail? How readily available are these results?

- **Potential Vulnerabilities**: Does the research highlight vulnerabilities or consolidate existing information in ways that highlight vulnerabilities in existing MCMs, public health approaches, or agricultural infrastructure? Research that highlights vulnerabilities could impede our ability to prepare for and respond to disease outbreaks that could impact public health, agriculture, food security, economic security, or national security.

- **Potential Consequences:** Given your responses to the preceding questions, how readily could the knowledge, information, products, or technologies from the research be used to threaten public health, agriculture, food security, economic security, or national security?

  When considering the potential consequences of the misuse of knowledge, information, technology, or products obtained from research, think broadly about the potential impacts on public health, agriculture, food security, economic security, or national

Box 1: Points to Consider in Assessing Research for its Dual Use Potential

security from the intentional misapplication of the results from the research in question. In general, information that could be misused to harm large populations of humans, plants, or animals; cause public panic; or require costly response efforts would be considered a greater risk.

- Consider the nature of the potential consequences (e.g., harm to public health, agriculture, food security, economic security, or national security) that might result from misuse of the research results in question. Information that could be misused to harm numerous sectors of society or the environment may be of greater concern.
- Consider the scope and magnitude of the potential consequences. Research or research information that could be misused to cause severe harm, disease, or consequences is generally considered to be of greater concern. Could the impact on people, animals, and/or plants be considered minor, moderate, or major?
- Consider the availability and efficacy of MCMs. Sufficient and efficacious MCMs could decrease concern about the consequences of misuse. MCMs may include drugs, biological products, public health practices, pesticides, or devices intended for diagnosis, detection, mitigation, prevention, or treatment.
    - Are there currently any MCMs to help mitigate the potential consequences of misuse?
    - Are the MCMs readily and widely available?
    - What are the impacts on the healthcare system when it comes to administering the MCMs?

Note: IRE and PIs are expected to be well-positioned to make technical assessments about how readily and in what ways certain knowledge, information, products, or technologies obtained from research might be misused.

Step 6b: Determine whether research should be designated Category 1.

To determine whether research should be designated as Category 1, IREs should assess whether the research, based on current understanding, constitutes DURC, as specified in Section 4.1.3 of the Policy. Careful consideration of the dual use risks associated with the research should underpin the determination of whether the research in question meets the definition of DURC.

- If the research is already considered Category 2 research, it is not Category 1 research. Dual use risk mitigation such as responsible research communication still applies and should be incorporated into the risk mitigation plan developed for the Category 2 research, as appropriate. Proceed to **Step 7** to notify the federal funding agency of Category determination.

- Based on the dual use risk assessment, if the research meets the definition of DURC, and is not already considered Category 2 research, designate the research as Category 1 and proceed to **Step 7** to notify the federal funding agency of Category determination.

- Based on the risk assessment carried out in Step 6a, if the research does NOT meet the definition of DURC, and is not designated as Category 2 research, then the research is not subject to additional institutional oversight and the IRE does not need to continue with the review. However, the IRE must proceed to **Step 7** to notify the appropriate federal funding agency of its findings. The PI should be informed that if at any time the reviewed research may meet the definition of Category 1 or Category 2 research, the PI should halt further work, refer the research again to the IRE for Category 1 or Category 2 review, and notify the federal funding agency.

E.3 Risk-Benefit Assessments, Risk Mitigation Plan, and Oversight of Category 1 or Category 2 Research

Step 7: Notify federal funding agency of Category determination.

- If the IRE determines that the research meets Category 1 or Category 2 designation, the IRE should inform the PI and funding agency of its findings and proceed with the review process, which includes drafting of risk-benefit assessments (proceed to **Step 8** and **Step 9**) and a risk mitigation plan (**Step 10**).

- If the IRE determines that the research does NOT meet Category 1 or Category 2 designation, the IRE must still inform the PI and the federal funding agency of these findings. However, no further actions are needed.

It is the responsibility of PIs and research institutions to identify research that may fall within scope of Category 1 or Category 2 research. Federal funding agencies have the discretion to request additional information or review of individual research proposals or projects to determine whether they may fall within scope of Category 1 or Category 2 research.

The research institution should notify the appropriate federal funding agency of the IRE's findings as soon as possible and no later than within 30 calendar days after the of the IRE's determination.

If significant concerns about Category designation remain, the Institutional Contact for Dual Use Research (ICDUR) should be informed. The ICDUR and the IRE may choose to consult with a representative of the federal funding agency.

Step 8: Assess the potential benefit

In order to determine the acceptable level of risk associated with Category 1 and Category 2 research and the best mitigation strategies, the research should be assessed for its potential benefits. There are many benefits inherent to scientific research, but it must be performed safely and securely. Such benefits may impact various sectors of society and be realized over different time frames. The points in **Box 2** below address some aspects of the research that could be considered, but they are not exhaustive. IREs should augment these points to fit their needs and the research under consideration.

Box 2: Points to Consider in Assessing the Benefits of the Category 1 and Category 2 Research
• What are the potential benefits to public health, agriculture, food security, economic security, or national security from the research? • What potential solution(s) does the research offer to an identified problem or vulnerability? • How would the research be useful to the scientific, public health, national security, or agriculture communities? • How will the knowledge, information, technology, or products generated from the research be broadly applicable (e.g., to human health, multiple scientific fields, populations of organisms)? • If a benefit has been identified, in what time frame (e.g., immediate, near future, years from now) might this research benefit public health, agriculture, food security, economic security, or national security?

Step 9: Develop risk-benefit assessments.

IREs should produce a risk-benefit assessment that assesses the potential benefits and the potential risks of the proposed research in a clear and thorough manner. Weighing the risks and benefits of Category 1 and Category 2 research can be challenging because risks and benefits are not always easily quantified in ways that are comparable.

The process of weighing the risks and benefits of Category 1 and Category 2 research is an exercise in making rational assessments, despite uncertainty. Uncertainty can best be managed by ensuring that the process draws on the expertise and perspectives of a group of individuals of diverse backgrounds and experience. Discussion and debate within such a group can help to (a) identify and mitigate the biases that individuals may inevitably bring to the challenges of this sort, (b) uncover assumptions in arguments, (c) scrutinize and test the basis for judgments, and (d) yield conclusions that represent a consensus and are optimally defensible.

In assessing risks, some assessments will entail judgments of feasibility that may be expressed in such phrases as "highly likely" or "less likely" rather than with quantitative measures (e.g., 90 percent or 10 percent). Others will be expressed in such phrases as "readily" or "very easily," or "with difficulty" or "with great difficulty." With still other assessments, the aim will be to project the possible consequences of the misuse of Category 1 and Category 2 research knowledge, information, products, or technologies and to describe the magnitude of these consequences (e.g., projected rates of morbidity and mortality —– in humans, animals, or plants —– due to infection with or exposure to biological agents or toxins). Such projections will often be based on or extrapolated from limited data and thus will be associated with varying degrees of uncertainty. In assessing the benefits, similar challenges will be encountered. It will be difficult to identify with precision the concrete benefits that can be reasonably expected to accrue from a particular body of Category 1 and Category 2 research and to project, with accuracy, the time frame within which those benefits could be realized. Judgments may also be expressed in qualitative rather than quantitative terms. They may be tempered with some degree of uncertainty.

Box 3 provides examples of are several questions that can be posed with respect to most Category 1 and Category 2 research that undergoes this process of risk-benefit assessment. The answers to these questions will inform the development of a risk mitigation plan.

Box 3: Points to Consider for Weighing the Risks and Benefits of Category 1 and Category 2 research

- Are there other ways in which the potential benefits of the research could be achieved that would reduce the anticipated risks?
- Could the knowledge, information, products, or technologies of concern be more readily applied to improvements in surveillance, development of MCMs, or other beneficial purposes than to malevolent applications? What reasons or evidence support the answer to this question?
- What is the time frame in which potential benefits might be realized? Does it rely on other research endeavors?
- How might the potential benefits and the anticipated risks be distributed across different human, animal, and plant communities? Who or what will be the likely beneficiaries of the potential benefits? Who or what will bear the anticipated risks? Is it likely that one or more specific populations will bear the burden of the anticipated risks?
- Considering the anticipated risks along with potential benefits, are the risks of such a feasibility and magnitude that they warrant proceeding after developing and implementing a risk mitigation plan? Are the potential benefits of significant magnitude to warrant proceeding despite the risks?
- What is the most responsible way to proceed? Do measures in the risk mitigation plan effectively and measurably reduce the anticipated risk?

Step 10: Develop a draft risk mitigation plan.

The risk-benefit assessments will be used by the PI and IRE to develop a draft risk mitigation plan. Both the risk-benefit assessments and the draft mitigation plan should be provided to the federal funding agency for review and approval within 90 calendar days from the IRE determination.

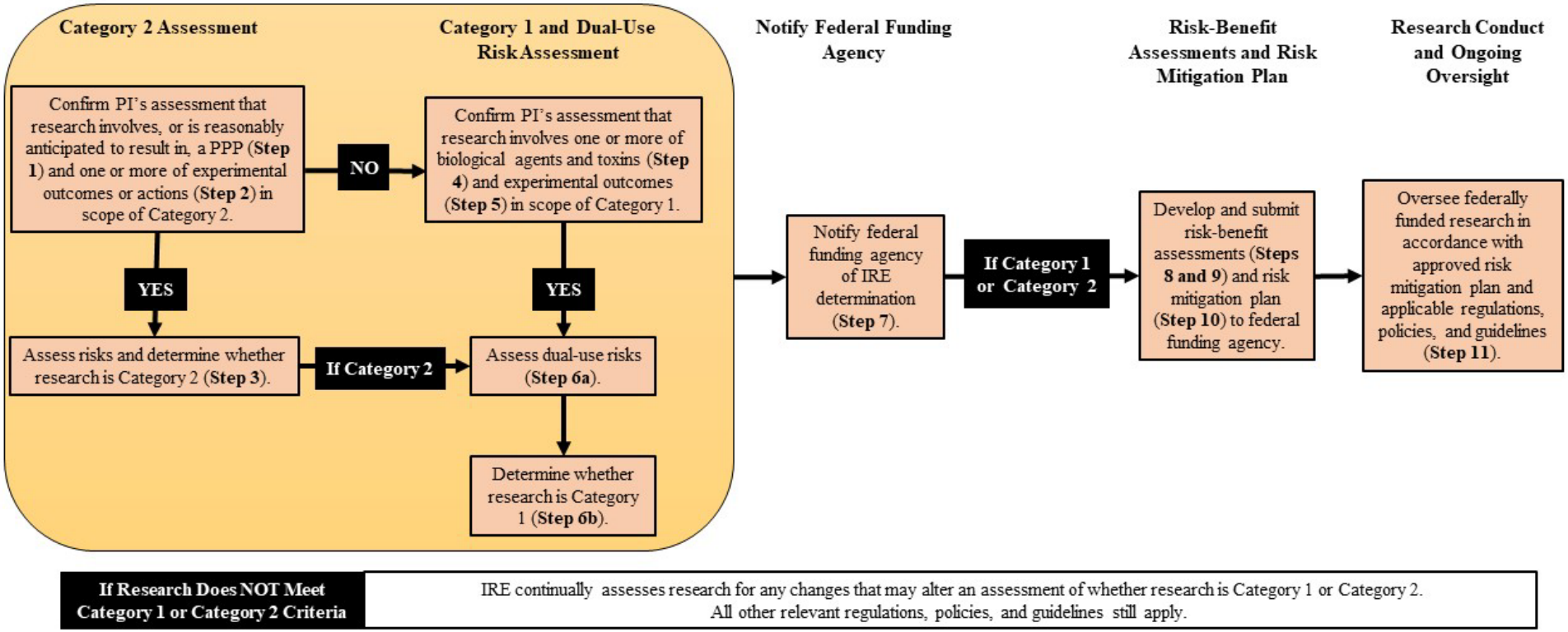
The IRE, along with the PI, should draft a risk mitigation plan and determine if additional measures are needed to mitigate risks associated with Category 1 or Category 2 research. Guidance for developing this risk mitigation plan is provided in Part F of this *Implementation Guidance*.

Step 11: Oversee the research.

Following approval of risk-benefit assessments and the risk mitigation plan by the federal funding agency, the IRE assists with and oversees the implementation of the risk mitigation plan. This includes ensuring that the research is conducted in accordance with the approved risk mitigation plan and is periodically reviewed by the research institution to determine if additional modifications to the risk mitigation plan are appropriate.

The IRE should also evaluate the risk mitigation plan at least annually and, working with the funding agency as appropriate, modify the plan as necessary for the duration of the research.

Figure 3. IRE Review Process for Category 1 or Category 2 Research. Depicts the IRE workflow for review and assessment of research that might be subject to the Policy.



F. GUIDANCE FOR INSTITUTIONAL REVIEW ENTITIES: DRAFTING RISK MITIGATION PLANS

F.1 Strategies for Developing a Draft Risk Mitigation Plan

It is important to consider the nature of the risks associated with Category 1 and Category 2 research prior to identifying strategies for mitigating those risks. Although risk assessments may be quantitative or qualitative, the assessment process outlined in Part E of this *Implementation Guidance* is, for the most part, qualitative in nature and requires consideration and judgment.

Some of the identified risks may be addressed by risk mitigation measures already in place. For example, some of the listed agents are regulated under the Federal Select Agent Program (FSAP), which requires appropriate biosafety and biosecurity oversight of specific biological agents and toxins that have the potential to pose a severe threat to human, animal, or plant health, or to animal and plant products. The *NIH Guidelines* and *BMBL* also contain biosafety and physical security provisions that may be applicable to research within scope of the Policy.

The biological agents generated by the Category 1 or Category 2 research being reviewed should have a designated management plan for their full life-cycle: from the time of creation, appropriate inventory and access controls, tracking (if transferred to or shared with third parties),[22] and ultimate safe destruction.

For each project containing research identified as Category 1 or Category 2 research, the Policy requires that where necessary, additional risk mitigation measures be proposed and instituted. The IRE should consider the strategies outlined in **Box 4** to determine the most appropriate risk mitigation measures that are tailored specifically to the research in question. These strategies are neither comprehensive nor mutually exclusive and may be used in combination. More than one strategy may be applicable for addressing a given risk.

Box 4: Menu of Risk Mitigation Measures that May Be Applicable to Your Research

Risk Mitigation Measures Already in Place at Your Institution

Use all applicable measures from this menu in your draft risk mitigation plan to summarize the risk mitigation measures that the IRE and/or PIs have identified as already in place and address the risks associated with the Category 1 and Category 2 research in question. Specify any others that are not listed.

- The research is being conducted in compliance with the select agent regulations (42 CFR part 73, 9 CFR part 121) biosafety and biosecurity requirements.

[22] Institutions should follow all applicable laws, regulations, and other requirements, guidelines, and best practices for the transfer and sharing of biological agents and toxins, some of which is summarized in the BMBL.

Box 4: Menu of Risk Mitigation Measures that May Be Applicable to Your Research

- The researchers are required by the terms and conditions of the grant or contract to adhere to the well-established biosafety and containment practices and procedures in the *NIH Guidelines*.
- The researchers are required by the terms and conditions of the grant or contract to adhere to the well-established biosafety and containment practices and procedures in BMBL.
- The researchers are required by the terms and conditions of the grant or contract to conduct the research at the appropriate BSL (and attest, with documentation if available, that the BSL facility is certified against appropriate standards to the appropriate level of containment, if not registered with the FSAP).
- The *NIH Guidelines* require that the biosafety aspects of the research be reviewed and approved (where appropriate) by an Institutional Biosafety Committee.
- The research has been reviewed for its Category 1 or Category 2 potential by an appropriately constituted IRE.
- The PI and researchers are required by the terms and conditions of the grant or contract to undergo training in the safe conduct of research with the biological agent(s) or toxin(s) in question.
- The researchers have a designated management plan for the full life-cycle a biological agent(s) or toxin(s) generated from the research; from time of creation, appropriate inventory and access controls, tracking (if transferred to or shared with third parties), and ultimate safe destruction.
- The researchers are required by the terms and conditions of the grant or contract to undergo training in the responsible conduct of research and/or research ethics as required by the institution and federal guidelines.
- The researchers are required by the terms and conditions of the grant or contract to be enrolled in an occupational health surveillance program, when appropriate.

Supplementary Risk Mitigation Measures that Could be Newly Implemented for Your Research

Select all applicable additional measures from this menu to summarize the risk mitigation measures that the IRE, or PIs, have identified as additional measures necessary to mitigate the risks associated with the Category 1 or Category 2 research in question. Specify any others that are not listed. These measures may be in place or proposed:

- Modify the design or conduct of the research to mitigate potential risks while achieving the benefits of the proposed research.

Box 4: Menu of Risk Mitigation Measures that May Be Applicable to Your Research

- Apply specific or enhanced biosafety and biosecurity measures.
- Evaluate MCM efficacy against biological agents or toxins resulting from Category 1 and/or Category 2 research prior to initiating research. Where effective MCMs exist and are readily and widely available, it may be useful to include that information in publications.
- Refer the institution to available educational tools for assessing and mitigating potential risks of the research.
- Regularly review, at the institutional level, emerging research findings for additional Category 1 and Category 2 research.
- Request that institutions notify federal funding agencies if additional Category 1 or Category 2 research is identified, and propose modifications to the risk mitigation plan, as needed.
- Determine the venue and mode of communication (addressing content, timing, and possibly the extent of distribution of the information) to communicate the research responsibly. See Part G of this *Implementation Guidance* for more information.
- Review annual progress reports from PIs to determine if Category 1 and Category 2 research results have been generated, and if so, flag them for institutional attention and additional mitigation measures as described above, as necessary. Progress reports may be required and reviewed with greater frequency, as commensurate with risk assessments.
- Develop a plan and methodologies for responsibly communicating the findings of the research, any time during the lifecycle of the project, including voluntary redaction of the research publications or communications. See Part G of this *Implementation Guidance* for more information.

If the risks posed by the project cannot be adequately mitigated with these measures, federal funding agencies should consider whether it is appropriate to:

- Request voluntary redaction of publications or communications resulting from the project.[23]
- Terminate or do not provide funding.

[23] Actions taken to restrict the publication of technology may have implications under export control laws and regulations (e.g., 15 CFR parts 730-774 and 22 CFR parts 120-130).

F.2 Elements of a Risk Mitigation Plan

Risk mitigation plans should provide sufficient details on the research subject to the Policy to enable the federal funding agency to adequately assess the research institution's plan for managing the risks associated with Category 1 and/or Category 2 research identified by the IRE.

Risk mitigation plans should include the following:

- The name and contact information for the PI(s).
- The name and contact information for the authorized institutional official – sometimes known as "the Responsible Official" when research involves biological select agents and toxins (BSAT).
- The name of the ICDUR (if different from the authorized institutional official).
- The dates and details of the reviews and assessments of the research by the IRE.
- The dates and details of the PI's initial review or ongoing assessment of the research.
- Identification of whether the research has been identified as Category 1 and/or Category 2 under the Policy.
- Details of the risks identified by the IRE in its review of the research, and an explanation of the risk mitigation strategy or strategies that are being implemented by the institution to address those risks.
- Other materials, such as proposals and progress reports related to the research, that may be requested by the federal government.

G. GUIDANCE FOR RESPONSIBLE COMMUNICATION OF CATEGORY 1 AND CATEGORY 2 RESEARCH FINDINGS

Open dissemination of research findings is an important principle of the scientific research enterprise. Open communication can provide vital, real-time information to researchers, clinicians, first responders, community members, and policymakers to that not only alerts communities to potential biological risks, but also lays the groundwork for devising effective MCMs and fostering scientific breakthroughs with substantial public health, agriculture, food security, economic security, or national security benefits. The life sciences landscape is now incredibly dynamic, with the rapid evolution of technologies, the ever-expanding reach of globalized research, the ease of information exchange, the a shifting landscape of avenues for scientific communication, and the growing awareness that entities may aim to misuse knowledge gained from life sciences research for malicious ends. Acknowledging these dynamics and risks, the adoption of responsible communication strategies at the onset of a research proposal are more effective in curbing these hazards compared to implementing them solely at the point of publication.

The tools in this part of the *Implementation Guidance* are intended to guide PIs, research institutions, and IREs in identifying and assessing the risks and benefits of communicating research information that may have dual use concerns. The information below may also be useful for scientific publishers. It includes a series of questions that can be considered as well as options for the communication of Category 1 and/or Category 2 research findings. The information below describes points to consider when assessing the risks and benefits of communicating Category 1 or Category 2 research findings. Responsible communication of results is part of the criteria that will be used by federal funding agencies in the review and approval of research subject to Category 2 oversight.

G.1 Assessing the Risks and Benefits of Communicating Research Findings

G.1.1 Risk-Benefit Analysis of Communication

Communication Risk Analysis

- Are there reasonably anticipated risks to public health, agriculture, food security, economic security, or national security from direct misapplication with no, or only minor, modification of the information that would be communicated?
    - Is novel information provided that could be misused to threaten public health, agriculture, food security, economic security, or national security?
    - Does the information point out vulnerabilities in public health, agriculture, food security, economic security, or national security preparedness and response?
    - Does the novel scientific information point out a gap in regulatory biosafety or biosecurity oversight or evade existing biosafety or biosecurity measures?
- How easy would it be for those who intend harm to use the information? For example:

    - What level of expertise and/or capability is required to reproduce the work described?

    - What is the availability of and access to the required expertise, technology, equipment, or reagents?

- Is it reasonably anticipated that this information could be directly misused with no, or only minor, modification to pose a threat to public health and safety, agricultural crops/ and other plants, animals, the environment, materiel, or national security?

- If a risk has been identified, in what time frame (e.g., immediate, near future, years from now) might this information be used to pose a threat to the public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security? What is the scope or magnitude of the potential risk(s) identified?

- Is it reasonably anticipated that there will be effective, implementable mitigation measures for the identified risk(s) ahead of the potential threat to the public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security, even if the time frame is years from now?

- If the information were to be broadly communicated "as is" or with specified modification(s), what would the potential be for the following:

    - Public anxiety (e.g., widespread concern about public health or other safety/security issues)?

    - Public misunderstanding, including its implications (e.g., psychological, social, economic, or commercial impacts, or impact on health or diet)?

    - Sensationalism (e.g., exaggeration of the potential benefits, risks, impacts) on the part of the authors/presenters or the media?

    - Are there other negative consequences that could be anticipated, such as a loss of public trust?

- If the information were to be communicated in a significantly abridged form, what would be the potential for the following:

    - Public anxiety (e.g., widespread concern about public health or other safety/security issues)?

    - Public misunderstanding, including its implications (e.g., psychological, social, economic, commercial impacts, or impact on health or diet decisions)?

    - Sensationalism (e.g., exaggeration of the potential benefits, risks, impacts) on the part of the authors/presenters or the media?

- Are there other negative consequences that could be anticipated, such as a loss of public trust?

Communication Benefit Analysis

- Are there potential benefits to the public health, agriculture, food security, economic security, or national security from the application or utilization of the communicated information?

- Are there potential benefits of the information for public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security? What is the scope or magnitude of the potential benefit(s) identified?

- Will this information be useful to the scientific community? If so, how?

- If a benefit has been identified, in what time frame (e.g., immediate, near future, years from now) might this information be used to benefit public health, agriculture, food security, economic security, or national security?

G.1.2 Considerations for Weighing Benefits and Risks of Communicating Research Findings

Consider the points below when assessing the risks and benefits associated with communicating Category 1 and/or Category 2 research findings and when formulating a communications plan:

- What information is provided?

- What are the novel aspects of the communication in terms of the following?

    - Results

    - Methods

    - Combining previously communicated information or methods in a novel fashion

    - Combining new information with some previously communicated information

- What is the "scientific context" of this information? For example, to what extent is similar information already publicly available?

    - To what extent has the new information already been communicated (e.g., through presentations and abstracts at scientific meetings, press releases or articles, or on the internet)?

    - Was this information previously communicated responsibly? Consider the risk and benefits of communicating potentially dual use information again and in a different context.

- How are the risks and benefits of communicating this information distributed across different stakeholders?
    - Who stands to benefit (e.g., large vs. small populations, vulnerable or low-resourced populations vs. well-resourced populations)?
    - Who bears the risk? Is the burden of risk disproportionate to one or more specific groups?
    - Is the distribution of the risks and benefits fair and just? If the distribution of risks and benefits is not the same, is there a way to extend the benefits more widely or to mitigate disproportionate risks?
- What is the time frame in which potential benefits or anticipated risks of the communication might be realized?
- Do the benefits of communicating the information outweigh the risks? If so, how? Alternatively, do the risks outweigh the benefits? If so, how?
- Could the information of concern be more readily applied to improvements in surveillance, development of MCMs, or other beneficial purposes than to malevolent applications? What reasons or evidence support the answer to this question?

G.1.3 Recommendations Regarding Responsible Communication of Research Findings

The risk-benefit analysis should inform development of a communication plan in which the research information is shared to the fullest extent possible in order to realize the potential benefits while effectively managing the risk of potential misuse of the information. After consideration of the risks and benefits of communicating the findings of Category 1 and/or Category 2 research methods and results, decisions about how to responsibly communicate that information should address the content, timing, and possible extent of distribution of the information.

Possible communication or publication actions (more than one may be applicable)

A. Communicate or publish as is.

B. Communicate or publish with addition of appropriate contextual information. For example, it may be important to address:

    i. The significance of the research findings for public health, agriculture, food security, economic security, or national security;

    ii. How the new information or technology will be useful to the scientific community and the public more broadly;

    iii. The types of biosafety and biosecurity measures in place as the research was conducted; and

iv. The careful assessment and consideration that was given to the concerns about risk of potential misuse of the information in the decision to publish.

C. Communicate or publish openly, but withhold specific information that is of concern. For example, is it possible to "decouple" the material that poses security concerns from some or all of the potentially useful scientific information, or should specific information be removed (e.g., technical details about an enabling technology or specificity of vulnerabilities)?

   i. Communicate information of concern through mechanisms where results or methods have access-control, with appropriate access request processes.

   ii. Delete certain information and then communicate or publish the remaining information openly.

D. Communicate only to selected parties (not openly communicated).

   i. Communicate to selected parties, specifying who they are and the mechanisms of communication.

   ii. Communicate selected information to selected parties, but the rest of the information is communicated only to the funding agency.

E. Do not disseminate the research results in any manner.

Consider timing of communication, based on considerations set forth above

A. Communicate immediately (to the extent decided above).

B. Defer communication (to the extent decided above) until a clearly defined and agreed-upon endpoint is reached (e.g., a condition is met such that the degree of risk is significantly lower).

Final consideration of the agreed-upon course for going forward

A. Does the proposed course of action mitigate, to an acceptable level, the risks that were identified in the risk-benefit analysis?

B. Are new risks introduced as a result of modifications? Are there new concerns or unintended consequences regarding the proposed communication? If so, what are they and can they be mitigated?

C. Is it likely that the proposed course of action will be challenging to implement or enforce? Is a contingency plan necessary? Would additional resources be required?

H. GUIDANCE FOR FEDERAL FUNDING AGENCIES: REVIEWING CATEGORY 1 AND CATEGORY 2 RESEARCH

Federal funding agencies[24] that fund or sponsor intramural or extramural research subject to the Policy will establish a multidisciplinary review entity to review proposed or ongoing research subject to the Policy. Federal funding agencies will implement the Policy based on their specific structure and are encouraged to implement review processes that enable reviews without unnecessary delays.

H.1 Guidance for Federal Funding Agencies for Reviewing Category 1 Research

A. Proposed research that is deemed to be scientifically meritorious by an independent internal or external review process and is being considered for funding by the federal funding agency must be referred to a federal funding agency-level multidisciplinary review entity if it meets the following conditions:

   i. Involves one or more of the biological agents or toxins within scope of Section 4.1.1 of the Policy;

   ii. Has been determined to be reasonably anticipated to result in one or more of the experimental outcomes listed in 4.1.2 of the Policy; and

   iii. The IRE has assessed the research and made a Category 1 determination.

B. The purpose of the federal funding agency-level or equivalent Category 1 review is to provide a multidisciplinary review and evaluation of proposed research that meets the scope of Category 1 research as outlined in Section 4.1 of the Policy, determine whether funding is appropriate, and, if so, to help inform funding agency decisions and identify the appropriate risk mitigation strategies, as needed. The federal funding agency will inform the research institution of the potential funding recommendation and the need for any additional documentation related to the Category 1 research review before a final funding determination is made. The following disciplines will be represented on the federal funding agency-level review entity: scientific research, biosafety, biosecurity and national security, and ethics, and other relevant areas.

C. The federal funding agency review entity will review the risk-benefit assessments and risk mitigation plan in concert with funding decisions. To the extent practicable, the agency review entities should complete the review process within 90 calendar days of receiving the risk-benefit assessments and draft risk mitigation plan for Category 1 research from the research institution.

[24] As defined in the Policy, a "federal funding agency" is a federal department, agency, institute, center, or office that funds or sponsors intramural or extramural research at research institutions in the United States or internationally, with pathogens or toxins where the research is within Category 1 or Category 2 under the Policy, as described in Section 4.

H.2 Guidance for Federal Funding Agencies for Reviewing Category 2 Research

A. Proposed research that is being considered for funding by the federal funding agency and is deemed to be scientifically meritorious by an independent internal or external review process must be referred to a department-level multidisciplinary review entity if it meets the following conditions:

   i. Involves, or is reasonably anticipated to result in, a PPP as specified in Section 4.2.1 of the Policy;

   ii. Has been determined to be reasonably anticipated to result in, or does result in, one or more of the experimental outcomes or actions specified in Section 4.2.2; and

   iii. The IRE has assessed the research and made a Category 2 determination

B. The purpose of the department-level or equivalent Category 2 review is to provide a multidisciplinary, pre-funding review and evaluation of proposed research that meets the scope as outlined in Section 4.2 of the Policy to recommend whether funding is appropriate, and if so, to help identify the appropriate risk mitigation strategies. The following expertise will be represented during the department-level review: scientific research, biosafety, biosecurity, MCM development and availability, law enforcement and national security, ethics, public health preparedness and response, biodefense, Select Agent Regulations, public health policy, and other relevant areas, as determined by the department. The department-level review group may include ex officio and/or ad hoc members from other federal departments and agencies as deemed appropriate by the department.

C. Federal funding agency review entities will refer for department-level review any proposed intramural or extramural research that meets the following conditions:

   i. It has been deemed to be scientifically meritorious;

   ii. It is being considered for funding; and

   iii. It has been designated as Category 2 research by the federal funding agency.

D. The funding agency will provide the following materials to the department-level multidisciplinary review entity:

   i. Information about the research necessary for the department-level multidisciplinary review entity to conduct the review;

   ii. Risk-benefit assessments developed by the research institution; and

   iii. A risk mitigation plan developed by the research institution.

E. The department-level multidisciplinary review entity or equivalent Category 2 research review entity may transmit the following recommendations to the federal funding agency:

   i. Research is acceptable for federal funding;

   ii. Research is not acceptable for federal funding;

   iii. Research is acceptable for federal funding on the condition that certain experiments are modified;

   iv. Research is acceptable for federal funding on the condition that certain risk mitigation measures are employed at the federal and/or institutional level; or

   v. Other recommendations, as deemed appropriate.

For research proposals that fail to meet the criteria for guiding federal funding decisions on proposed Category 2 research as specified in Section 5.3.E of the Policy, the department-level multidisciplinary review entity will recommend that the research is not acceptable for federal funding.

I. GUIDANCE FOR DEPARTMENT-LEVEL MULTIDISCIPLINARY REVIEW ENTITY FOR CATEGORY 2 RESEARCH

The department-level multidisciplinary review entity is meant to provide multidisciplinary expertise and perspectives to an evaluation of the proposed Category 2 research, including the associated risk-benefit assessments and proposed risk mitigation plan, and to provide relevant feedback and/or comments to inform federal funding agency funding decisions.

The department-level review of proposed Category 2 research will be based on the following criteria:

- The research has been evaluated by an expert review process and has been determined to be scientifically sound (i.e., the federal funding agency has already deemed this research appropriate for funding);
- An assessment of the overall potential risks and benefits associated with the research determines that the potential benefits as compared to the potential risks to society are justified;
- There are no feasible, equally efficacious alternative methods to address the same question in a manner that poses less risk than does the proposed approach;
- The PI and the research institution where the research would be carried out have the demonstrated capacity, capability, and commitment to conduct it safely and securely, and have the ability to notify the funding agency, respond rapidly, mitigate potential risks

and take corrective actions in response to laboratory accidents, lapses in protocol and procedures, and potential security breaches;

- The research results are anticipated to be responsibly communicated, in compliance with applicable laws, regulations, and policies, and any terms and conditions of funding, in order to realize their potential benefit;

- The research will be supported through funding mechanisms that allow for appropriate management of risks and ongoing federal and institutional oversight of all aspects of the research throughout the course of the research; and

- The research is ethically justifiable. Non-maleficence, beneficence, justice, respect for persons, scientific freedom, and responsible stewardship are among the ethical values that should be considered by a multidisciplinary review process in making decisions about whether to fund research involving a PEPP, or an eradicated or extinct PPP that may pose a significant threat to public health, the capacity of health systems to function, or national security.

The department-level multidisciplinary review entity will be responsible for:

- Critically evaluating the research, including the institution's risk-benefit assessments and risk mitigation plan that guides the conduct of the research and communication of the research outcomes;

- Requesting, to a reasonable extent, additional relevant materials related to the research that may inform its evaluation;

- Advising on what, if any, additional risk mitigation measures and/or additional ongoing oversight features may be needed;

- Notifying the research institution, via the federal funding agency, of concerns or disagreements with a risk mitigation plan and review changes submitted by the institutions;

- Developing recommendations on acceptability for funding, including suggestions for additional risk mitigation measures and/or terms and conditions of award, if funded; and

- Reviewing any unexpected outcomes identified by federal funding agency reviews of progress reports throughout the funding period.[25]

[25] Where biosafety or biosecurity concerns arise during this period, including unexpected research outcomes (which may be predefined by the department-level review process, e.g., enhanced pathogenicity above a specified threshold), the federal funding agency will communicate these to the department-level multidisciplinary review entity. The department-level multidisciplinary review entity will have the discretion to decide whether the concerns or outcomes warrant convening another department-level review to consider whether to recommend further mitigation measures or a different recommendation about the appropriateness of agency funding are appropriate.

The department-level review of Category 2 research will result in recommendations to the federal funding agency; however, the final funding decisions will be made by the federal funding agency. The federal funding agency will advise the department-level multidisciplinary review entity of its intention to fund at least 72 hours in advance of invoking commencing procedures to fund the proposed research. The department of the funding agency will note in its records of any substantive deviations from the recommendations made by the department-level multidisciplinary review entity to the funding agency.

J. FURTHER VOLUNTARY GUIDANCE FOR POLICY IMPLEMENTATION

J.1 Criteria for Consulting Federal Funding Agencies

It is expected that IREs are able to develop plans for the responsible conduct and communication of Category 1 and Category 2 findings in the risk mitigation plans. However, there may be some situations in which consultation with the federal funding agency may be helpful.

The federal funding agency may be consulted by institutions (not by individual researchers) for cases where:

A. Unique expertise (e.g., on national security) is needed to assess the potential risks associated with the conduct and communication of the research;

B. The IRE requires guidance on developing an adequate risk mitigation strategy for communication in cases where the potential risks of communication are perceived as particularly high;

C. The IRE considers the only viable risk mitigation strategy to be not conducting the research in question or not communicating its findings;

D. The PI whose research has been reviewed does not agree with the IRE's findings, and the institution would like to request outside advice; or

E. The research in question represents a particularly complex case or appears to fall outside the definition of Category 1 or Category 2 but still seems to present significant concerns.

J.2 Voluntary Guidance for *In Silico* Models and Computational Approaches

The scope of the Policy does not cover *in silico* research. However, the rapidly evolving nature of computational biology and the increasing use of computational models and approaches, including the use of artificial intelligence, can potentially contribute to the production of dual-use biological knowledge, information, technologies, and products, just as *in vivo* or *in vitro* Category 1 or Category 2 research outlined in the Policy. As outlined in the Policy, PIs and IREs are encouraged to, on a voluntary basis, conduct similar assessments of the benefits and risks of *in silico* research, specifically the development of potential dual-use computational models that can directly enable the design of a PEPP or a novel biological

agent or toxin, and implement risk mitigation measures as appropriate. For example, this would include modeling tools designed to predict nucleic acid or amino acid modifications anticipated to enhance the virulence or transmissibility characteristics, or likelihood of immune evasion, e.g., antibody escape, of a PEPP or novel or mutated PPP upon synthesis.

Researchers developing or considering the development of tools meeting these specifications, or other *in silico* tools that appear to have comparable risks, are encouraged to assess the capacity of such models and computational approaches to be misused, such as with the set of questions recommended in Part D and Part E of this *Implementation Guidance*, to determine a safe and secure way to proceed with the given line of study and responsible communication of the results, models, and datasets. Possible responses to proposed research involving the *in silico* production of dual use data could include full publication, partial publication, or no publication, as described in Part G.1.3 of this *Implementation Guidance*.

Best practices for this rapidly evolving field of study remain under development. Researchers and research institutions seeking additional guidance on the benefits and risks of *in silico* research are encouraged to consult the federal funding agency on a voluntary basis to discuss any questions or concerns. Such discussions may inform continued development of guidance tailored to the benefits and risks unique to *in silico* research. Researchers and research institutions should also consider consulting with their security and information technology offices as applicable to mitigate physical security and cyber security risks, respectively, in developing a risk mitigation measures.

APPENDIX A: POLICY DEFINITIONS

The definitions provided below are from Section 3 of the Policy:

A. "*Biological agents*" are any microorganism (including, but not limited to, bacteria, viruses, fungi, or protozoa), infectious material, or any naturally occurring, bioengineered, or synthesized component of any such microorganism or infectious material, capable of causing:
   - Death, disease, or other biological malfunction in a human, an animal, a plant, or another living organism;
   - Deterioration of food, water, equipment, supplies, or material of any kind; or,
   - Deleterious alteration of the environment.

B. "*Biosafety*" is the application of practices, controls, and containment infrastructure that reduces the risk of unintentional exposure to, contamination with, release of, or harm from pathogens, toxins, and other associated biological materials.

C. "*Biosecurity*" is the application of security measures designed to prevent the loss, theft, misuse, diversion, unauthorized possession or material introduction, or intentional release of pathogens, toxins, biological materials, and related information and/or technology.

D. "*Dual use research*" is research conducted for legitimate purposes that generates knowledge, information, technologies, and/or products that can be utilized for benevolent or harmful purposes.

E. "*Dual use research of concern (DURC)*" is life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be misapplied to do harm with no, or only minor, modification to pose a significant threat with potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security.

F. *"Federal funding agency*" is a federal department, agency, institute, center, or office that funds or sponsors intramural or extramural research at research institutions in the United States or internationally, with pathogens or toxins where the research is within Category 1 or Category 2 under the Policy, as described in Section 4.

G. "*Institutional Contact for Dual Use Research (ICDUR)*" is the official designated by the research institution to serve as an internal resource for application of the Policy as well as the liaison (as necessary) between the institution and the relevant federal funding agency.

H. "*Institutional review entity (IRE)*" is the entity established by the research institution to execute the institutional oversight responsibilities described in Section 5.2, with the attributes described in Section 5.2.B.

I. "*Life sciences*" is the study or use of living organisms, viruses, or their products, including all disciplines, methodologies, and applications of biology (including biotechnology, genomics, proteomics, bioinformatics, and pharmaceutical and biomedical research and techniques).

J. "*Pathogen with enhanced pandemic potential (PEPP)*" is a type of pathogen with pandemic potential (PPP) resulting from experiments that enhance a pathogen's transmissibility[26] or virulence, or disrupt the effectiveness of pre-existing immunity, regardless of its progenitor agent, such that it may pose a significant threat to public health, the capacity of health systems to function, or national security. Wild-type pathogens that are circulating in or have been recovered from nature are not PEPPs, but may be considered PPPs because of their pandemic potential.

K. "*Pathogen with pandemic potential (PPP)*" is a pathogen that is likely capable of wide and uncontrollable spread in a human population and would likely cause moderate to severe disease and/or mortality in humans.[27]

L. "*Principal investigator*" (PI) is the senior/key person seeking or receiving federal research and development funding (i.e., extramural funding). This includes researchers at federal agency laboratories and facilities, as well as researchers at government-owned, contractor-operated laboratories and facilities (i.e., intramural researchers, whether or not federally employed). There may be more than one PI on a research grant or project within a single or multiple institution(s).

M. "*Reasonably anticipated*" describes an assessment of an outcome such that, generally, individuals with scientific expertise relevant to the research in question would expect this outcome to occur with a non-trivial likelihood. It does not require high confidence that the outcome will definitely occur, but excludes experiments in which experts would anticipate the outcome to be technically possible, but highly unlikely.

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[26] Experiments that enhance a pathogen's transmissibility (as listed in Section 4.2.2.i of the Policy) include those that enhance environmental stability of the pathogen or toxin or change the tropism or host range of the pathogen or toxin in a way that enables an increased ability to infect and transmit between humans, among others.

[27] Pathogens with pandemic potential are often those with little to no pre-existing immunity in the human population.

N. "*Research institution*" is any academic institution, corporation, company, partnership, society, association, firm, sole proprietorship, government agency, or other legal entity that conducts life sciences research.

APPENDIX B: REFERENCED DOCUMENTS

- Biosafety in Microbiological and Biomedical Laboratories 6th Edition (June 2020), https://www.cdc.gov/labs/BMBL.html.

- "Framework for Nucleic Acid Synthesis Screening," (April 2024), https://www.whitehouse.gov/wp-content/uploads/2024/04/Nucleic-Acid_Synthesis_Screening_Framework.pdf.

- National Biodefense Strategy and Implementation Plan (2022), https://www.whitehouse.gov/wp-content/uploads/2022/10/National-Biodefense-Strategy-and-Implementation-Plan-Final.pdf.

- National Security Memorandum on Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security. (2022), https://www.whitehouse.gov/briefing-room/presidential-actions/2022/10/18/national-security-memorandum-on-countering-biological-threats-enhancing-pandemic-preparedness-and-achieving-global-health-security/.

- NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (April 2024), https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf

- Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (2017), https://aspr.hhs.gov/S3/Documents/P3CO-FinalGuidanceStatement.pdf.

- United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential (May 2024).

- United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern (2014), https://aspr.hhs.gov/S3/Documents/durc-policy.pdf.

- United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern (2012), https://aspr.hhs.gov/S3/Documents/us-policy-durc-032812.pdf.

APPENDIX C: CATEGORY 1 LIST OF BIOLOGICAL AGENTS AND TOXINS

Section 4.1 of the Policy provides for Category 1 review for research on any biological agent or toxin in the following list (from Section 4.1.1 of the Policy), where the research is reasonably anticipated to result in one of the experimental outcomes outlined in Section 4.1.2 of the Policy and where the research constitutes DURC as specified in Section 4.1.3 of the Policy:

- All Select Agents and Toxins listed in 9 CFR 121.3–121.4, 42 CFR 73.3–73.4, and 7 CFR 331.3 and regulated by USDA and/or HHS.
- All Risk Group 4 pathogens listed in Appendix B of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) - Classification of Human Etiologic Agents on the Basis of Hazard.
- A subset of Risk Group 3 pathogens listed in Appendix B of the NIH Guidelines - Classification of Human Etiologic Agents on the Basis of Hazard.
- For biological agents affecting humans that have not been assigned a Risk Group in the NIH Guidelines, refer to the current edition of Biosafety in Microbiological and Biomedical Laboratories (BMBL). In such cases, agents affecting humans that are recommended to be handled at Biosafety Level 3 (BSL-3) or Biosafety Level 4 (BSL-4) per the BMBL guidance are subject to this Policy.
- Biological agents added during future updates to the Implementation Guidance as specified in Sections 7 and 8.

The checklist below is a list of the particular biological agents and toxins that are generally described above and under Section 4.1.1 of the Policy, as of the date of this *Implementation Guidance*. This checklist is provided as an implementation tool for identifying research that may require Category 1 review. It is important to note that this checklist is subject to change depending upon amendments to the source documents listed above, including the BSAT list managed by HHS and USDA, and the Risk Group 3 and Risk Group 4 designations managed by NIH. Thus, it is always prudent to consult the original sources to confirm that your biological agent or toxin of interest is or is not subject to Category 1 review. It is encouraged, on a voluntary basis, to apply this *Implementation Guidance* and assess DURC risks even if the biological agent of interest is not one from the source documents. When questions arise regarding particular strains of pathogens, please refer to the BSAT list, the *NIH Guidelines*, or the BMBL, as appropriate.[28]

As described further in Section 6 of the Policy, there may be additional types of life sciences research that do not involve these biological agents or toxins described in Section 4.1.1 of the Policy or experiments in Section 4.1.2 of the Policy, yet pose DURC risks as described in

[28] For the purposes of the Policy, where a pathogen is both a Select Agent and a Risk Group 3 or Risk Group 4 biological agent, the strain exclusions under the FSAP supersede those specified in the *NIH Guidelines*.

Section 4.1.3 of the Policy. PIs and research institutions are encouraged to remain vigilant to such research, including work involving any other pathogen or toxin regardless of its Risk Group, and develop and apply appropriate risk mitigation measures.

HHS Select Agents and Toxins[29]	
☐	Abrin
☐	*Bacillus cereus* Biovar *anthracis*
☐	Botulinum neurotoxins
☐	*Clostridium botulinum* and neurotoxin-producing species of *Clostridia*
☐	Conotoxins (Short, paralytic alpha conotoxins containing the following amino acid sequence $X_1CCX_2PACGX_3X_4X_5X_6CX_7$)
☐	*Coxiella burnetii*
☐	Crimean-Congo hemorrhagic fever virus
☐	Diacetoxyscirpenol
☐	Eastern equine encephalitis virus
☐	Ebola virus
☐	*Francisella tularensis*
☐	Lassa fever virus
☐	Lujo virus
☐	Marburg virus
☐	Mpox virus Clade I
☐	1918-1919 H1N1 including reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (Reconstructed 1918 Influenza virus)
☐	Ricin
☐	*Rickettsia prowazekii*
☐	Severe acute respiratory coronavirus (SARS-CoV)
☐	SARS-CoV/SARS-CoV-2 chimeric viruses resulting from any deliberate manipulation of SARS-CoV-2 to incorporate nucleic acids coding for SARS-CoV virulence factors
☐	Saxitoxin

[29] Biological agents and toxins listed in this part of the list are controlled by Select Agent Regulations, please refer to the Select Agents and Toxins list for any relevant strain exclusions.

☐	Chapare virus
☐	Guanarito virus
☐	Junín virus
☐	Machupo virus
☐	Sabía virus
☐	Staphylococcal enterotoxins (subtypes A, B, C, D, E)
☐	T-2 toxin
☐	Tetrodotoxin
☐	Tick-borne encephalitis complex virus: Far Eastern subtype
☐	Tick-borne encephalitis complex virus: Siberian subtype
☐	Kyasanur Forest disease virus
☐	Omsk hemorrhagic fever virus
☐	Variola major virus (Smallpox virus)
☐	Variola minor virus (Alastrim)
☐	*Yersinia pestis*
Overlap Select Agents and Toxins	
☐	*Bacillus anthracis*
☐	*Bacillus anthracis* Pasteur strain
☐	*Brucella abortus*
☐	*Brucella melitensis*
☐	*Brucella suis*
☐	*Burkholderia mallei*
☐	*Burkholderia pseudomallei*
☐	Hendra virus
☐	Nipah virus
☐	Rift Valley fever virus
☐	Venezuelan equine encephalitis virus
USDA Veterinary Services (VS) Select Agents and Toxins	
☐	African horse sickness virus

☐	African swine fever virus
☐	Avian influenza virus [this is included here as a veterinary select agent in 9 CFR 121.3. Low pathogenicity strains are excluded.]
☐	Classical swine fever virus
☐	Foot-and-mouth disease virus
☐	Goat pox virus
☐	Lumpy skin disease virus
☐	*Mycoplasma capricolum*
☐	*Mycoplasma mycoides*
☐	Newcastle disease virus
☐	Peste des petits ruminants virus
☐	Rinderpest virus
☐	Sheep pox virus
☐	Swine vesicular disease virus
USDA Plant Protection and Quarantine (PPQ) Select Agents and Toxins	
☐	*Coniothyrium glycines*
☐	*Peronosclerospora philippinensis (Peronosclerospora sacchari)*
☐	*Ralstonia solanacearum*
☐	*Rathayibacter toxicus*
☐	*Sclerophthora rayssiae*
☐	*Synchytrium endobioticum*
☐	*Xanthomonas oryzae*
Other Risk Group 4 Pathogens[30]	
☐	Tick-borne encephalitis virus complex including Absetterov, Central European encephalitis, Hanzalova, Hypr, and Kumlinge
☐	Herpesvirus simiae (herpes B or monkey B virus)
☐	Hemorrhagic fever agents and viruses as yet undefined

[30] Pathogens listed in this part of the list are Risk Group 4 but not controlled by the Select Agent Regulations, please refer to the *NIH Guidelines* for any relevant strain exclusions.

Other Risk Group 3 Pathogens[31]	
☐	*Bartonella*
☐	Brucella
☐	*Orientia tsutsugamushi*
☐	*Pasteurella multocida* type B -"buffalo" and other virulent strains
☐	*Rickettsia akari*, *R. australis*, *R. canada*, *R. conorii*, *R. rickettsii*, *R, siberica*, *R. typhi* (*R. mooseri*)
☐	Chikungunya virus except the vaccine strain 181/25
☐	Semliki Forest virus
☐	St. Louis encephalitis virus
☐	Flexal virus
☐	Lymphocytic choriomeningitis virus (LCM) (neurotropic strains)
☐	Hantaviruses, including Hantaan virus
☐	Middle East respiratory syndrome coronavirus (MERS-CoV)
☐	Severe acute respiratory coronavirus 2 (SARS-CoV-2)
☐	Japanese encephalitis virus except strain SA 14-14-2
☐	West Nile virus
☐	Yellow fever virus
☐	Human influenza A virus H2N2 (1957-1968)
☐	Highly pathogenic avian influenza A virus H5Nx strains within the Goose/Guangdong/96-like H5 lineage (e.g., H5N1, H5N6, H5N8 etc.)
☐	Transmissible spongiform encephalopathy (TSE) agents (e.g., Creutzfeldt-Jacob disease and kuru agents)
Other	
☐	Any attenuated pathogen or vaccine strain that is currently excluded from the Select Agent Regulations that exhibits the recovery of virulence at or near the wild-type
☐	Mpox virus clade I/II chimeric viruses resulting from any deliberate manipulation of clade II to incorporate nucleic acids coding for clade I virulence factors

[31] Pathogens listed in this part of the list are Risk Group 3 but not controlled by the Select Agent Regulations, please refer to the *NIH Guidelines* for any relevant strain exclusions.

APPENDIX D: EXAMPLE SCENARIOS: ASSESSMENT OF CATEGORY 1 AND CATEGORY 2 RESEARCH

Examples of Research that would be Considered for Category 1 Assessment

The following set of examples describes hypothetical research experiments that would likely require additional review and oversight as outlined under Category 1 of the Policy. The examples describe the Category 1 review process including PI identification, IRE assessment, and submission of that assessment to the federal funding agency.

Example A: Research on Yersinia pestis

Background*: Yersinia pestis*, the causative agent responsible for plague, likely emerged < 6000 years ago from an enteric bacterial ancestor. Along with genome-level changes, a specific set of mutations has contributed to the emergence of *Y. pestis* by allowing it to thrive inside a flea vector and maximize its flea-borne transmission to mammalian hosts (primarily rodents), causing severe disease, including in humans. Some of these mutations on specific genes have led to *Y. pestis* being able to form a sticky layer (e.g., a biofilm) that adheres to the gut of the insect and facilitates biofilm dependent transmission (BDT). BDT occurs when the *Y. pestis* biofilm begins to interfere with or block normal blood feeding, triggering regurgitation of infectious blood into the bite site.

Research Study: Understanding the role of biofilms in pathogen transmission may lead to insights into how to control plague. In this study, a research group proposes to further explore vector competence on different rodent host species and plans to examine a *Y. pestis* gene that is hypothesized to be involved with biofilm production. The researchers hypothesize that some of the genetic changes observed on the gene potentially contribute to the increased transmission of *Y. pestis* to rodent hosts.

To explore this, they propose to generate *Y. pestis* strains that differentially express this gene and test each strain's ability to form biofilms in flea guts and to transmit the pathogen to a rodent host. They hypothesize that strains overexpressing this gene will produce biofilm faster and more effectively, thereby increasing *Y. pestis* transmission in rodents.

Research Review Process: *Y. pestis* is a biological select agent and is thus within scope of Category 1 assessment as outlined in Section 4.1.1 of the Policy and the *Implementation Guidance* Appendix C checklist. The study is also reasonably anticipated to result in an experimental outcome outlined in Section 4.1.2 of the Policy (e.g., Increase transmissibility of a pathogen within or between host species). While the PI is aware that *Y. pestis* was once a pandemic pathogen, modern public health systems and MCMs greatly diminish the pathogen's ability to spread uncontrollably such that it is not currently considered a PPP in a wild-type or a modified form and thus would not require Category 2 assessment. The PI moves forward with Category 1 review process. The PI will submit information to the funding agency and IRE detailing the Category 1 pathogen under investigation (e.g., *Y. pestis*) and the relevant experimental outcome(s) (e.g., Increase transmissibility of a

pathogen within or between host species). The IRE would determine if the proposed research meets the threshold for Category 1 designation by examining if the proposed research (1) involves an agent on the Category 1 list, (2) is reasonably anticipated to result in the experimental outcome, and (3) meets the definition of DURC. The IRE would document their assessment and Category 1 determination and transmit this information to the federal funding agency when requested.

Risk Mitigation: The PI could mitigate associated risks of this experiment by applying enhanced biosafety and biosecurity measures or by modifying the design of the research to work with attenuated versions of *Y. pestis* strains, among other measures that they would detail in their risk mitigation plan as requested by the IRE and federal funding agency (see full menu of possible risk mitigation measures in Part F of this *Implementation Guidance*).

Example B: Research on Botulinum neurotoxin producing species of Clostridium

Research Study: A PI creates a novel expression system using a native *Clostridium* spp host to recombinantly express a new botulinum neurotoxin (BoNT) serotype for the purpose of toxin purification and full characterization. This Clostridial expression system has been engineered to both remove the native BoNT gene structure and to overexpress the new BoNT present on a plasmid, and still express the other toxin associated proteins (hemagglutinins, and non-toxin non-hemagglutinin).

This new recombinant strain was shown to overexpress recombinant BoNT relative to wild-type native *C. botulinum* strains. The choice to use a native *C. botulinum* host for expression was based on the required translation and post-translational processing machinery and cellular environment, all of which are needed to produce a fully active and stable toxin complex. The virulence and susceptibility to countermeasures of the newly expressed BoNT serotype has not yet been fully characterized, but preliminary experiments indicate that the newly expressed BoNT serotype is likely more toxic due to changes in post- translational modifications observed in other more toxic serotypes.

Review Process: Botulinum neurotoxins and botulinum neurotoxin producing species of Clostridium are biological select agents and toxins, and are thus within scope of Category 1 assessment as outlined in Section 4.1.1 of the Policy and the *Implementation Guidance* Appendix C checklist. The PI also reasonably expects the research to meet one of the listed experimental outcomes, namely to increase the toxicity of a known toxin or produce a novel toxin. The PI for the study will submit information to the funding agency and IRE detailing the biological agent and toxin under investigation (e.g., Botulinum neurotoxin producing species of Clostridium and novel toxin serotype) and the expected experimental outcome(s) (e.g., increase the toxicity of a known toxin or produce a novel toxin). The IRE would determine if the proposed research meets the threshold for Category 1 designation by examining if the proposed research (1) involves an agent on the Category 1 list, (2) is reasonably anticipated to result in the experimental outcome, and (3) meets the definition of DURC. The IRE would document their assessment and Category 1 determination and

transmit this information to the federal funding agency when requested. Separately, the PI must also submit this proposal to the FSAP, as the proposed experiment is within scope of restricted experiments with biological select agents and toxins requiring FSAP approval and funding agency approval, as needed.

Risk Mitigation: The PI could mitigate the associated risks by applying enhanced biosafety and biosecurity measures and by developing a plan and methodology for responsibly communicating the findings of the research, among other measures (see full menu of possible risk mitigation measures in Part F of this *Implementation Guidance*). The PI could also mitigate associated risks of this experiment by modifying the design of the research to use an expression system in a native *Clostridium* spp host. In addition, because this is within scope of restricted experiments with biological select agents and toxins, there may be additional risk mitigation measures prescribed by the FSAP should the PI be permitted to conduct the proposed experiment.

Example C: Research on Monkeypox virus

Background: Strains of the zoonotic pathogen Monkeypox virus (MPXV) falls into two main clades. MPXV clade I has a higher case fatality rate (CFR) (~11% in unvaccinated; during the outbreak in DRC which started in 2023, the CFR is ~4.6%) and is a biological select agent, while MPXV clade II has a significantly lower-case fatality rate (<1%) and is not regulated by the FSAP.

Research Study: A researcher is interested in understanding if incorporating an immune evasion gene from MPXV clade I will confer higher morbidity and mortality to MPXV clade II. The researcher proposes genetically modifying MPXV clade II to insert the immune evasion gene from MPXV clade I.

Review Process: This research involves a clade I-clade II MPXV chimera in which an immune evasion gene from MPXV clade I that has >95% genetic identity to MPXV clade I is being inserted within a MPXV clade II strain with the reasonable anticipation of increasing the virulence of MPXV clade II in an animal model. As such, this research is subject to Category 1 assessment as outlined in Section 4.1.1 of the Policy and would require review by the IRE. The PI would submit the study for IRE review outlining the pathogen(s) under investigation (e.g., MPXV clade I-MPXV clade II recombinant virus) and the expected experimental outcomes (e.g., increase the virulence of a pathogen or convey virulence to a non-pathogen; alter a human or veterinary biological agent to disrupt the effectiveness of pre-existing immunity, via immunization or natural infection, against the biological agent). The IRE would determine if the proposed research (1) involves an agent on the Category 1 list, (2) is reasonably anticipated to result in the experimental outcome, and (3) meets the definition of DURC. The IRE would document their assessment and transmit the information to the federal funding agency when requested.

Risk Mitigation: The PI could mitigate risks by regularly reviewing experimental findings to assess how virulence compares between the MPXV clade I-MPXV clade II recombinant virus and the MPXV clade I virus. The PI could also develop a plan for responsibly communicating the findings of the research and potentially protect the data from public release if warranted, among other measures (see full menu of possible risk mitigation measures in Part F of this *Implementation Guidance*). In addition, there may be additional risk mitigation measures prescribed by the FSAP.

Example D: Research on Yellow Fever Virus

Background: Yellow Fever Virus (YFV) is transmitted via mosquito bites and can cause epidemics of potentially fatal hemorrhagic fever. The YFV 17D vaccine, available since 1938, is recommended by WHO for routine immunization in the regions where is YFV prevalent to prevent and control outbreaks. However, there are no approved or authorized therapeutics for YFV.

Research Study: A researcher is interested in understanding YFV evasion of 17D vaccine-induced immune responses and proposes to assess this by employing serial passaging of the wild-type YFV in the presence of serum samples from vaccinated subjects to produce a set of immune-escaped YFV variants. The researcher will then identify the amino acid residues associated with escape from neutralizing antibodies employed in their selection. The researcher anticipates that the YFV variants selected in the presence of sera may have a reduced susceptibility to the YFV-specific protective immunoglobulins, rendering the approved and authorized 17D vaccine ineffective.

The same researcher is also interested in studying mechanisms of resistance of YFV to antiviral candidates in clinical development and decides to assess this by employing serial passaging of the wild-type YFV in the presence of antiviral candidates to select for antiviral-resistant YFV variants. The researcher anticipates that YFV variants selected in the presence of antiviral candidates may have a reduced susceptibility to the tested drug candidates such that they will be able to identify mutations that confer antiviral resistance that can help identify future molecular targets for clinical development.

Review Process: YFV is a Risk Group 3 pathogen within scope of Category 1 assessment as outlined in Section 4.1.1 of the Policy and the *Implementation Guidance* Appendix C checklist. The PI also reasonably expects the research to meet several listed experimental outcomes: increase resistance of a biological agent to clinical and/or veterinary prophylactic or therapeutic interventions; and alter a human or veterinary biological agent to disrupt the effectiveness of pre-existing immunity, via immunization or natural infection, against the biological agent. Thus, the PI for the study will submit information to the funding agency and IRE detailing the pathogen(s) under investigation (e.g., Yellow Fever Virus) and the expected experimental outcome(s) listed above. The IRE would determine if the proposed research meets the threshold for Category 1 designation by examining if the

proposed research (1) involves an agent on the Category 1 list, (2) is reasonably anticipated to result in the experimental outcome, and (3) meets the definition of DURC. The IRE would document their assessment and Category 1 determination and transmit this information to the federal funding agency when requested.

In this case, the IRE may determine that some aspects of the proposed research meet the DURC threshold for Category 1 designation, while others do not. For example, selecting YFV variants under the presence of sera are in scope of Category 1. However, the IRE may consider that experiments selecting YFV variants in the presence of investigational antiviral candidates are not in scope of Category 1, because there is no approved or authorized therapeutics for YFV.

Risk Mitigation: The PI could mitigate the associated risks by regularly reviewing emerging research findings for additional Category 1 and Category 2 research, educating and training staff using available educational tools, and developing a plan and methodologies for responsibly communicating the findings of the research, among other measures (see full menu of possible risk mitigation measures in Part F of this *Implementation Guidance*).

Example E: Research on **Ralstonia solanacearum**

Background: Many plant pathogens have an asymptomatic or latent period after infection. Plants that do not show immediate symptoms upon infection by a plant pathogen are said to have a latent infection. For example, bacterial wilt infections, caused by strains belonging to the *Ralstonia solanacearum* species complex, can cause latent infections (i.e., bacterial colonization of plant vascular elements with limited or no wilting).

Research Study: A PI would like to understand the determinants of latent infection in plant-microbe interactions. Promising candidate genes have been identified that could be causal in this latent infection and/or the pathogenicity of the bacterium *Ralstonia solanacearum*. To understand the molecular and physiological basis of plant defense evasion, the researchers intend to knockout or overexpress these candidate genes and test them in the laboratory and in the greenhouse. The researcher hypothesizes that these mutations may enhance the pathogenicity of this plant pathogen that infects major, economically important plant species (e.g., potato, tomato, and other solanaceous crops). This bacterium is also responsible for many indirect costs including restriction of trade in potentially infected plants.

Review Process: *Ralstonia solanacearum* is a USDA Plant Protection and Quarantine (PPQ) Select Agents and Toxins within scope of Category 1 assessment as outlined in Section 4.1.1 of the Policy and the *Implementation Guidance* Appendix C checklist. The PI for the study will submit information to the funding agency and IRE detailing the pathogen(s) under investigation (e.g., *Ralstonia solanacearum*) and the expected experimental outcome(s) (e.g., increase the virulence of a pathogen or convey virulence to a non-pathogen or the ability of a pathogen to cause disease). The IRE would determine if the proposed research

meets the threshold for Category 1 designation by examining if the proposed research (1) involves an agent on the Category 1 list, (2) is reasonably anticipated to result in the experimental outcome, and (3) constitutes DURC. The IRE would document their assessment and Category 1 determination and transmit this information to the federal funding agency when requested.

Risk Mitigation: The PI could mitigate the associated risks by applying enhanced biosafety and biosecurity measures and by developing a plan and methodology for responsibly communicating the findings of the research, among other measures (see full menu of possible risk mitigation measures in Part F of this *Implementation Guidance*).

Examples of Research that would be Considered for Category 2 Assessment

The following set of examples describe hypothetical research experiments that would likely require additional review and oversight as outlined under Category 2 research of the Policy. The examples describe the Category 2 review process from PI identification, to IRE assessment, to submission of that assessment to the federal funding agency.

Example F: Research on Coronaviruses

Research Study: A laboratory is interested in understanding the molecular determinants of coronavirus transmissibility. To understand which genes are involved in transmissibility, the researchers intend to introduce mutations in viral proteins of a replication-competent, wild-type MERS-CoV and assess the impact on viral replication and transmission. Resulting mutant viral strains will be assessed for growth kinetics in cultured cells and used for infection experiments in *in vivo* models of transmissibility. The researchers hypothesize that mutating certain regions of the viral genome is reasonably anticipated to enhance transmissibility relative to wild-type MERS-CoV. The experimental objective is to identify amino acid residues in MERS-CoV that are associated with transmissibility and enable better understanding of the transmissibility potential of other zoonotic merbecoviruses.

Review Process: The proposed research will involve a PPP as the starting pathogen and the resulting modified PPP is reasonably expected to have increased transmissibility and virulence characteristics relative to its wild-type. The PI therefore determines that it is appropriate for additional review to determine whether it constitutes Category 2 research. The PI submits information to the IRE detailing the anticipated resulting pathogen under investigation (e. g., the PPP, a modified MERS-CoV) and the expected experimental outcome(s) anticipated on the pathogen (e.g., enhance transmissibility of the pathogen in humans). The IRE would determine if the proposed research meets the threshold for Category 2 designation by examining if the proposed research (1) involves a PPP, or any pathogen that will be modified in such a way that is reasonably anticipated to result in a PPP, (2) is reasonably anticipated to involve a Category 2 experimental outcome or action, and (3) is reasonably anticipated to result in the development, use, or transfer of a PEPP or

an eradicated or extinct PPP that poses significant threat to public health, the capacity of health systems to function, or national security. The IRE would document their assessment and Category 2 determination and transmit this information to the federal funding agency when requested. The funding agency would evaluate and verify the IRE's determination and subsequently refer the research and associated materials to their department-level Category 2 multidisciplinary review entity for their input into the appropriateness of funding the research, and, if applicable, any recommended changes to the experimental plan or risk mitigation plan to help ensure that it is conducted safely and securely.

Risk Mitigation: The PI could mitigate associated risks by applying enhanced biosafety and biosecurity measures, training research staff using available educational tools, and developing a plan and methodology to responsibly communicate research findings. The PI could also consider studying these mutations in *in silico* model systems, pseudovirus strains, attenuated MERS strains, or by using recombinant proteins, among other measures (see full menu of possible risk mitigation measures in Part F of this *Implementation Guidance*).

Note: If the IRE or funding agency determine that the research does not meet the threshold for Category 2 research designation, the research may still need to be assessed for DURC risks and Category 1 designation.

Example G: Research on Seasonal Influenza

Research Study: A researcher is interested in investigating if they can attenuate seasonal influenza strains for use as vaccines by suppressing elements of the innate immune system. They plan to do this by incorporating interfering RNA transcripts (RNAi) into the seasonal influenza virus genome. RNAi are short RNA transcripts homologous to cellular genes that lead to the suppression of those genes through recruiting an endogenous ribonuclease to the dsRNA they form when binding to homologous cellular transcripts. This results in the cleavage of the transcript and efficient suppression of those genes. The researcher has designed short RNAi transcripts to add to their seasonal influenza vaccine candidates. They intend to screen these modified viral strains in an animal model, followed by identification of viruses exhibiting decreased cytokine storm responses. The PI assesses that while these RNAi insertions are intended to suppress a cytokine storm response to potentially result in attenuated seasonal influenza viruses as vaccine candidates, the suppression of these innate immune genes may be reasonably anticipated to result in a virus strain that is immune evasive and thus potentially more pathogenic than the wild-type strain. Since these influenza virus strains are already very transmissible and may end up being more pathogenic due to this manipulation, the PI is concerned that the product of their experiments to create a vaccine attenuated strain could result in a PEPP.

Review Process: While experiments with seasonal influenza do not normally require enhanced oversight (i.e., neither Category 1 nor Category 2 is required for most experiments with seasonal influenza viruses), the PI remains vigilant for when their

experiments might have outcomes that would require enhanced biosafety or biosecurity oversight outlined in the Policy. Here, the proposed research involves an extreme form of genetic alteration of viruses that would not naturally occur, and that could lead to outcomes very different from those associated with standard seasonal influenza viruses, in that the expected experimental outcomes could enhance the pathogen in a manner that would be reasonably anticipated to give it the characteristics of a PEPP (e.g., enhance the immune evasion of the pathogen in humans such as by modifying the pathogen to disrupt the effectiveness of pre-existing immunity via immunization or natural infection). In this case, the PI assesses that their research may reasonably result in a PPP due to potential enhanced immune evasion and enhanced virulence. Therefore, the PI submits information to the IRE detailing the anticipated pathogen under investigation (e.g., a PPP, an enhanced seasonal influenza) and the expected experimental outcomes that could enhance the pathogen in a manner that would be reasonably anticipated to give it the characteristics that meet the definition of PPP. The IRE would determine if the proposed research meets the threshold for Category 2 designation by examining if the proposed research (1) involves a PPP, or any pathogen that will be modified in such a way that is reasonably anticipated to result in a PPP, (2) is reasonably anticipated to involve Category 2 experimental outcome or action, and (3) is reasonably anticipated to result in the development, use, or transfer of a PEPP or an eradicated or extinct PPP that poses significant threat to public health, the capacity of health systems to function, or national security. The IRE would then document their assessment and Category determination for submission to the funding agency. The funding agency would evaluate and verify the IRE's determination of the need for Category 2 oversight, and subsequently refer the research and associated materials to their department-level Category 2 multidisciplinary review entity for their input into the appropriateness of funding the research, and if applicable, any recommended changes to the experimental plan or risk mitigation plan.

Risk Mitigation: The PI could mitigate associated risks by applying enhanced biosafety and biosecurity measures, by training research staff using available educational tools, and by regularly reviewing emerging research findings for additional Category 1 and Category 2 considerations, among other measures (see full menu of possible risk mitigation measures in Part F of this *Implementation Guidance*).

Note: If the IRE or funding agency determine that the research does not meet the threshold for Category 2 research designation, the research may still warrant assessment and mitigation of DURC risks.

Examples of Research that would NOT be Considered for Category 1 or Category 2 Assessment

The following set of examples describe hypothetical research experiments that would likely NOT require additional Category 1 or Category 2 review and oversight as outlined by the Policy.

Example H: Adenovirus Drug Development

Background: Viral envelope glycoproteins are a primary determinant of host cell tropism, and investigations into their function have led to the development of treatments for several important diseases. Some researchers use chimeric viral systems (e.g., pseudotyped lentiviruses), in which envelope glycoproteins from one virus are co-expressed in cultured mammalian cells expressing capsids from another enveloped virus to generate replication deficient viruses with the interior components from one virus and the envelope glycoproteins from another. Viral genes encoding the capsid and envelope glycoproteins that are expressed by these cells can be excluded from the resulting viruses, making the viruses in such studies unable to produce a second round of viral progeny after an initial cell is infected. The resulting replication incompetent pseudotyped virus can be much safer to study in the laboratory than the glycoproteins in the parent virus. A small molecule (Drug A) initially developed as a treatment for cytomegalovirus infection has successfully completed Phase I human safety studies. Drug A also shows antiviral activity for adenoviruses (HAdV) and is an attractive clinical candidate for treating adenovirus-associated diseases in adults and children. Additional preclinical experiments are required for clinical development of Drug A as an HAdV therapy.

Research Study: The investigator proposes to evaluate resistance to Drug A by selecting for HAdV4 Drug A-resistant mutants through sequential rounds of virus replication in increasing concentrations of Drug A. Resistant isolates will be sequenced and identified mutations will be inserted into recombinant HAdV5 viruses to evaluate their role in resistance. The research may result in a virus that is more resistant to this Phase 2-ready clinical treatment. These types of resistance experiments are used as part of mechanism of action studies and to understand what mutations may occur in the virus when the drug is administered.

Review Process: Adenovirus is not a pathogen that is within scope of Category 1 (see Appendix C of this *Implementation Guidance* for the full checklist). However, because the experiment could result in increased resistance to clinical prophylactic or therapeutic interventions, the PI voluntarily and proactively submits information to the IRE detailing the pathogen under investigation and the relevant potential experimental outcomes(s) to see if additional institutional review and risk mitigation may be warranted. The IRE assesses that the research is not subject to Category 1 assessment because it does not involve an agent on the Category 1 list. The IRE determines that the proposed experiment to develop resistance pathways for Drug A does not impact resistance to approved

therapeutics and thus the research does not require additional risk mitigation measures at the institutional level.

Risk Mitigation: No additional risk mitigation likely needed beyond regular biosafety and biosecurity practices and procedures for HAdV5 viruses as outlined in the *NIH Guidelines*.

Other examples of research activities with PPPs that are outside the scope of the Policy, do not constitute enhancement research to create a PEPP, and would not meet the assessment criteria to be Category 2 include:

Example: SARS-CoV-2 variant surveillance activities, including collection of diagnostic and clinical specimens, sampling, sequencing, and basic viral characterization, in which the virus is not manipulated to enhance transmissibility, enhance virulence, or disrupt the effectiveness of pre-existing immunity in humans.

Example: Basic viral characterization studies of a novel beta coronavirus isolated from wild animal in the United States in which the virus is not manipulated to enhance transmissibility, enhance virulence, or disrupt the effectiveness of pre-existing immunity in humans. This would include pseudotype virus studies, receptor binding studies, animal model susceptibility studies, and *in vitro* experiments with cell lines or primary cells that do not involve serial passage, beyond what is required for viral isolation and characterization.

Example: Developing novel H7N9 vaccine strains for vaccine production such as the generation of high-growth attenuated strains for viral particle replication in chicken eggs, or qualified cell lines, or the generation of attenuated strains that confer improved antigenicity.

APPENDIX E: FREQUENTLY ASKED QUESTIONS ON U.S. GOVERNMENT POLICY FOR OVERSIGHT OF DUAL USE RESEARCH OF CONCERN AND PATHOGENS WITH ENHANCED PANDEMIC POTENTIAL (THE POLICY)

Q: Why is the federal government issuing the Policy?

A: The intent of the Policy is to strengthen oversight of life sciences research with pathogens and toxins throughout the research lifecycle by:

- Defining an expanded scope of biological agent and toxin research subject to additional oversight at the federal and institutional levels;
- Providing a unified framework to support the consistent identification and oversight of research that requires enhanced oversight that accounts for safety, security, and ethical considerations; and
- Delineating the roles and responsibilities of PIs, research institutions, and federal departments and agencies that conduct, fund, or oversee research within the scope of the Policy, with an emphasis on institutional oversight and management of this research.

The Policy outlines measures to ensure that potential biosafety and biosecurity risks are mitigated and research is carried out safely and securely. These measures are applied in a manner commensurate with risk in order to minimize adverse impacts on legitimate research and preserve and foster the benefits of research.

Q: How does the Policy relate to the 2017 P3CO Framework, 2012 DURC Policy, and 2014 DURC Policy?

A: The Policy addresses oversight for certain research on biological agents and toxins that, when enhanced, have the potential to pose risks to public health, agriculture, food security, economic security, or national security. It supersedes the 2012 United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern (Federal DURC Policy),[32] the 2014 United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern (Institutional DURC Policy),[33] and the 2017 Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO Framework).[34]

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[32] United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern. (2012) https://aspr.hhs.gov/S3/Documents/us-policy-durc-032812.pdf.

[33] United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern (2014) https://aspr.hhs.gov/S3/Documents/durc-policy.pdf.

[34] Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (2017) https://aspr.hhs.gov/S3/Documents/P3CO-FinalGuidanceStatement.pdf

Q: How does the Policy relate to the Federal Select Agent Regulations?

A: Select agents are those biological agents and toxins specifically identified in U.S. Department of Health and Human Services (HHS), Centers for Disease Control and Prevention (CDC) and U.S. Department of Agriculture (USDA), Animal and Plant Health Inspection Services (APHIS) regulations as having the potential to pose a severe threat to human, animal, or plant health, or to animal or plant products (for further information see 42 CFR Part 73, 7 CFR Part 331 and 9 CFR Part 121). Some of the biological agents and toxins included within the scope of the Policy are biological agents and toxins regulated by HHS CDC and USDA APHIS as a select agents.

The oversight system for DURC established by the Policy complements the Federal Select Agent Program. Both are based on principles and practices for reducing the likelihood that knowledge, information, products, or technologies emanating from research are intentionally misused to pose a significant threat with potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security.

Nothing in the Policy should be read as superseding any federal statutory authority, including those applicable to the U.S. Department of Health and Human Services, the U.S. Department of Agriculture, and any other federal department or agency, to regulate the possession, use, or transfer of biological select agents and toxins.

Q: To what type of research institutions does the Policy apply?

A: The Policy applies to research institutions in the United States and internationally that receive U.S. federal funding for research on biological agents or toxins that are subject to the Policy as described in Section 1.2 of the Policy.

Q: How will federal funding agencies implement the research oversight framework?

A: Federal funding agencies that fund research subject to the Policy will require all research institutions that they fund to fully follow the Policy, implement the Policy under statutory authorities applicable to them, and develop and promote consistent processes to the maximum extent appropriate. Implementation mechanisms may include, but are not limited to, terms and conditions of funding awards, and engaging in rulemaking to develop and implement new award requirements for contractors and other funding recipients, including regarding the sharing and reporting of information under the Policy.

Research institutions that do not receive any federal funds for life sciences research, but that nevertheless conduct life sciences research with identifiable biosafety or biosecurity risks, are strongly encouraged to implement oversight procedures consistent with the culture of shared responsibility underpinning the Policy.

Q: Why does the Policy include plant pathogens when it didn't previously?

A: Biological threats affecting humans, animals, or plants can cause harm to health and well-being and economic and supply chain disruption. Implementing a coordinated One Health[35] approach is a best practice for understanding, communicating, and mitigating biological threats swiftly and efficiently. Such an approach is necessary to rapidly and effectively assess, prevent, prepare for, respond to, and recover from biothreats, and mitigating potential nationally or internationally significant biological incidents.

Q: Does the Policy apply to all federally funded research or just research funded by HHS agencies (e.g., NIH, ASPR, FDA, CDC, etc.)?

A: The Policy is a unified federal oversight framework for conducting and managing certain types of federally funded life sciences research on biological agents and toxins that applies to all departments and agencies that fund research covered by the Policy. The Policy addresses oversight for research on biological agents and toxins that, when enhanced, have the potential to pose risks to public health, agriculture, food security, economic security, or national security.

OSTP issues the Policy and all federal departments and agencies will update, modernize, or promulgate applicable implementing guidance consistent with the Policy. The purpose of this government-wide policy is to enable consistent implementation of oversight across federally funded research.

Q: Why are pathogens included based on Risk Group? Why are some Risk Group 3 pathogens included and not others?

A: In order to aid in effective and consistent implementation of this expanded Policy scope, the U.S. government sought to develop a risk-based approach that would be familiar to the research community. With that in mind, the Policy leverages existing risk assessments by the *NIH Guidelines* to inform what types of biological agents and toxins are within scope of the Policy beyond the select aAgent and tToxins.

Risk Group 4 pathogens are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are not usually available. Risk Group 3 pathogens are associated with serious or lethal human disease for which preventive or therapeutic interventions may be available. It was determined that research with Risk Group 3 or Risk Group 4 pathogens resulting in experimental outcomes that could potentially lead to biosecurity or biosafety risks would be well served by mitigation measures in the Policy.

[35] One Health refers to a collaborative, multisectoral, and transdisciplinary approach at the local, regional, national, and global levels, with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and the environment.

The Risk Group 3 pathogens that were excluded from the oversight Policy generally have multiple safeguards that significantly reduce risk of any listed experimental outcome from becoming a significant threat to public health, agriculture, food security, economic security, or national security, if misapplied. For example, such safeguards may include several classes of drugs for treatment with different mechanisms of action, difficulties to grow or genetically manipulate the agent, and/or a combination of low transmissibility, virulence, and/or high population immunity.

Q: Why does the Policy change the definition of ePPP to PEPP?

A: The new term and its associated definition is meant to provide clarity that any pathogen, even if it does not start with pandemic potential, would be covered under the Policy if it underwent experiments reasonably anticipated to generate a pathogen with enhanced pandemic potential (PEPP).

Q: What is the difference between Category 1 and Category 2 research? Why are there different types of review for Category 1 and Category 2 research?

A: The Policy establishes a tiered system of review, with higher risk research requiring more oversight. The first tier, Category 1, describes "dual use research of concern" involving certain biological agents or toxins and experiments that could generate knowledge, information, technologies, or products that could be misused to pose a significant threat. The Policy requires institutions and federal funding agencies to provide oversight of Category 1 research. The second tier, Category 2, describes a smaller set of higher risk experiments, which involve or could generate "pathogens with enhanced pandemic potential" that could themselves pose a significant threat to the public. Due to the higher risk, the Policy requires institutions, federal funding agencies, and the federal departments overseeing those federal funding agencies to provide oversight of Category 2 research.

Q: Why are some pathogens included in the scope of both Category 1 and Category 2 research?

A: There may be research with a pathogen that poses heightened risk due to its potential to generate a PEPP by enhancing transmissibility, virulence, or immune evasion. Other forms of research with that same pathogen may not pose similar levels of heightened immediate societal risk but could still produce knowledge, information, technologies, or products that could be misused.

In those situations where *both* the risk of generating a PEPP and misuse of knowledge, information, technologies, or products exist, the pathogen should undergo the second tier of oversight, Category 2, which requires institutions, federal funding agencies, and the federal department overseeing those federal funding agencies to provide oversight of these experiments.

In those situations where the heightened risk of generating a PEPP is absent but there is risk of misuse of knowledge, information, technologies, or products, research with the pathogen should undergo the first tier of oversight, Category 1, which requires institutions and federal funding agencies to provide oversight of these experiments.

Q: Does the Policy require reporting of projects that are identified as Category 1 or Category 2 research after the initial proposal stage?

A: The Policy covers the research proposal stage and the full life cycle of the research, so at any point during the experimental process, PIs, IREs, and research institutions should be vigilant for emerging risks that may not have been anticipated.

Q: Is there a specific point of contact within the U.S. government for addressing questions about interpreting and implementing the Policy?

A: The federal funding agency from which you are seeking federal funding for research with biological agents or toxins would be the best POC for addressing questions about interpreting and implementing the Policy. OSTP is working with federal departments and agencies to coordinate consistent implementation across federal government.

Q: *How should risk-benefit assessments and risk mitigation strategies be developed for research that is funded by multiple federal funding agencies?*

A: The Policy recognizes there may be cases in which a federal department or agency simply passes through funding from another federal department or agency to support life sciences research at an institution that conducts or sponsors research involving Category 1 or Category 2 research. In this instance, the federal department or agency originally providing the funding is considered the federal funding agency, and the ultimate recipient of the funds is considered the research institution, and they respectively carry out the roles of each under the Policy. Pass-through agencies should be made aware of the Policy and associated requirements, and support the federal funding agency if requested.

Q: How should risk-benefit assessments and risk mitigation strategies be developed for research that is conducted by multiple research institutions?

A: The Policy recognizes there will be situations where elements of potential Category 1 or Category 2 research are being carried out at multiple research institutions through a subaward with a primary institution that directly receives an award from the federal funding agency. In cases of such collaborations involving multiple institutions via a subaward, the primary institution is considered the research institution in the Policy and is responsible for notifying the federal funding agency of research determined to be Category 1 or Category 2, and providing copies of each institution's risk mitigation plan or a single plan with relevant components. Furthermore, any subawardees participating in the collaboration, both foreign and domestic, should follow with the oversight framework under the Policy, and the primary

institution should ensure that Category 1 or Category 2 research oversight is consistently applied by all entities participating in the collaboration, e.g., through inclusion of appropriate requirements in the terms of the subaward.

Q: How does the Policy apply to research that is not federally funded?

A: Where a federal department or agency is authorized to establish oversight requirements on non-federally funded life sciences research as a condition of receiving federal funding, the federal department or agency should establish that U.S. research institutions attest to the federal government that they are implementing oversight of non-federally funded Category 1 and Category 2 research in accordance with the research oversight framework under this Policy.

Research institutions that do not receive any federal funds for life sciences research, but that nevertheless conduct life sciences research with identifiable biosafety or biosecurity risks, are strongly encouraged to implement oversight procedures consistent with the culture of shared responsibility underpinning this Policy. The U.S. government will consider additional approaches outside of this Policy for promoting use of these or similar oversight procedures by research institutions that conduct life sciences research and do not receive federal funding.

Q: Whose responsibility is it to identify and assess whether research requires Category 1 or Category 2 review and oversight?

A: Oversight is a shared responsibility among researchers, research institutions including IREs, and federal funding agencies. It is primarily the responsibility of investigators and institutions to identify research that falls within scope of Category 1 or Category 2. PIs are responsible for continuously reviewing their research to identify research that may be in scope of Category 1 or Category 2, notifying the funding agency, and referring the research to the IRE. The IRE works with the PI to conduct risk-benefit assessments as needed and determine if research meets the definition of DURC, and thus requires Category 1 oversight, and/or meets the definition of PEPP research, and thus requires Category 2 oversight. Federal funding agencies review institutional assessments and have the discretion to request additional information or review of individual research proposals or projects to determine whether they may fall within scope of Category 1 and/or Category 2 research.

Q: If a project with a biological agent or toxin listed in Category 1 scope is identified that includes experiments that are anticipated to produce any of the listed outcomes, is that project automatically considered Category 1?

A: No, a project may result in one or more of the listed experimental outcomes and still not be considered Category 1. Projects that are anticipated to result in the one or more of the listed experimental outcomes must then be assessed to determine whether they meet the definition of DURC.

Q: The policy states that OSTP and National Security Council staff, in consultation with relevant departments and agencies, will coordinate a process for identifying countries posing risks in which the U.S. government should not fund Category 1 and Category 2 research. Which countries have been identified through this process?

A: At the time of release of the Policy, the federal government will not fund Category 1 or Category 2 research in the following countries: the Democratic People's Republic of Korea (DPRK), the Islamic Republic of Iran, the Russian Federation, the People's Republic of China (along with the Special Administrative Regions of Hong Kong and Macau, for the purposes of this policy), Cuba, Syria, and Venezuela. This policy will be revisited and updated, as necessary. Departments may make exceptions on a case-by-case basis in exceptional circumstances. Please direct questions regarding research funding for proposals that would be affected by this policy to the relevant federal funding agency.

Q: How does the federal government plan to ensure that the Policy remains responsive to emerging biotechnology risks?

A: At least every four years, OSTP, in consultation with relevant departments and agencies, will review the Policy and update it as necessary and appropriate, to ensure that it adequately considers risks from DURC and research that may be reasonably anticipated to involve the creation, transfer, or use of PEPPs. This review will take into consideration the benefits of such research and the mitigation of risks, consistent with 42 U.S.C. § 6627(a)(1)(B). At least every two years, OSTP, in consultation with relevant departments and agencies, may review this Implementation Guidance to the Policy including the associated lists of biological agents and toxins and update it as needed.

Review and revision of the Policy and Implementation Guidance will consider benefits and risks arising from emerging scientific and technological advances and any implementation challenges. Future revisions of the Policy and this associated Implementation Guidance may be informed by inputs from interested communities, including scientists; national security officials; public health officials; state, local, tribal, and territorial officials; global health specialists; and the general public, as well as engagement with international partners, as appropriate.