

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.

