PROPOSED BIOSECURITY OVERSIGHT FRAMEWORK FOR THE FUTURE OF SCIENCE

Draft Findings & Recommendations of Two National Science Advisory Board for Biosecurity Working Groups

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Executive Summary

Life sciences research involving pathogens serves a critical role in pandemic preparedness and in ensuring that the United States and the global community are prepared to rapidly detect, respond to, and recover from biological threats, whether naturally occurring, accidental, or deliberate in origin. However, there are biosafety and biosecurity risks associated with undertaking research involving pathogens which include the possibility of laboratory accidents and the deliberate misuse of the information or products generated.

The United States (U.S.) has established a biosafety, biocontainment, and biosecurity oversight system[1] designed to protect laboratory workers, public health, agriculture, the environment, and national security. Periodic reassessment of our biosafety and biosecurity oversight frameworks helps to ensure that they effectively address existing and emerging safety and security concerns while continuing to support scientific progress and innovation. To help inform such efforts, in February 2022 the U.S. Government (USG) charged the NSABB with evaluating and providing recommendations on the effectiveness of two major U.S. biosecurity policy frameworks governing:

- Research with enhanced potential pandemic pathogens (PPPs), including the White House Office of Science and Technology Policy (OSTP) *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)*[2], and the *Department of Health and Human Services (HHS) Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens*[3]; and

- Dual Use Research of Concern (DURC), including the *USG Policy for Oversight of Life Sciences DURC*[4] and the *USG Policy for Institutional Oversight of Life Sciences DURC*[5].

In developing the findings and recommendations presented in this report, the two NSABB Working Groups tasked with evaluating the P3CO and DURC oversight frameworks and considered relevant policies and guidance, and consulted with subject matter experts in pathogen research, research administration and oversight, biosafety and biosecurity, biodefense, and national security, among others, from the USG, federal funding agencies, academic institutions, and scientific and professional societies. The Working Groups also considered public comments.

NSABB Working Group Findings on P3CO (Phase 1) & DURC (Phase 2) Oversight Frameworks

Phase 1 Findings

Finding 1. The current definitions of a PPP and enhanced PPP (ePPP) are too narrow. Overemphasis on pathogens that are both likely "highly" transmissible and likely "highly" virulent

[1] https://www.phe.gov/s3/Documents/FESAP-guiding-principles.pdf
[2] https://www.phe.gov/s3/dualuse/Pages/ppp-oversight-recommendations.aspx
[3] https://www.phe.gov/s3/dualuse/Documents/P3CO.pdf
[4] https://www.phe.gov/s3/dualuse/Documents/us-policy-durc-032812.pdf
[5] https://www.phe.gov/s3/dualuse/Documents/durc-policy.pdf

could result in overlooking some research involving the creation, transfer, or use of pathogens with enhanced potential to cause a pandemic.

Finding 2. Assessments for the identification of ePPP research must be focused on the potential for an activity or a modification to involve or produce a pathogen that meets the characteristics for an ePPP and not on the specific experimental approach or method to be undertaken.

Finding 3. Current P3CO policy does not adequately include roles for investigators and institutions in the identification, review, and ongoing oversight of ePPP research.

Finding 4. The additional review process outlined under the P3CO framework is generally appropriate. However, implementation directives and guidance to funding agencies, research institutions, and investigators are needed to facilitate more consistent and efficient implementation and ongoing oversight.

Finding 5. The review group constituted by HHS appears to have the appropriate expertise and the process is designed to protect potentially sensitive personal and proprietary information and facilitates open discussion. However, increased transparency in the review process is needed to engender public trust in the review and oversight processes.

Finding 6. The focus of the current P3CO framework on pathogens that are likely to cause disease in humans is appropriate. However, an analogous oversight framework is lacking for research involving enhanced animal or plant pathogens.

Finding 7. Global collaboration is vital to U.S. pandemic preparedness and response and broader global health security. Support for international ePPP research by the U.S. should be coupled to processes equivalent to requirements that govern domestic research in the U.S.

Phase 2 Findings

Finding 8. USG DURC policies appear to have achieved the original intent to establish and strengthen a shared system of review and oversight between the federal and local institutional levels to identify DURC and mitigate potential risks. However, the scope of the framework limits its success to a small fraction of the life sciences research enterprise.

Finding 9. A determination of whether research meets the definition of DURC requires assessments based on the best available information at the time but will often entail uncertainty.

Finding 10. The current scope of the DURC policies is limited, and the list-based approach to oversight is inherently less adaptive than other potential approaches. Some institutions have voluntarily expanded the scope of research reviewed for potential DURC to include the entirety of their pathogen research portfolios. However, this entails an additional burden of review that varies based on the nature and size of the institution's or funding agency's pathogen research portfolio.

Finding 11. Responsible communication of research methods and results is a central component of mitigating risks associated with DURC. Most of the research subject to the DURC policies is

fundamental research and the findings are intended to, and can be, communicated responsibly if identified early in the research life cycle and adequate consideration is given to the timing, modes, and venues of communication, among other risk mitigation measures.

Finding 12. The potential biosafety and biosecurity risks associated with ePPP research and DURC justify USG efforts to introduce oversight of relevant research activities, regardless of the funding source.

Finding 13. There are substantive overlaps between the DURC and ePPP oversight frameworks, including the overarching intents, as well as the entities involved in policy implementation. Current differences between the frameworks, including the timing of the initial assessments and the roles for investigators and institutions need to be reconciled.

NSABB Working Group Recommendations on P3CO & DURC Oversight Frameworks to the U. S. Government

Phase 1 Recommendations

Recommendation 1. Amend USG P3CO policy to clarify that federal department-level review is required for research that is reasonably anticipated to enhance the transmissibility and/or virulence of any pathogen (i.e., PPPs and non-PPPs) such that the resulting pathogen is reasonably anticipated to exhibit the following characteristics that meet the definition of a PPP:

- Likely moderately or highly transmissible and likely capable of wide and uncontrollable spread in human populations; and/or
- Likely moderately or highly virulent and likely to cause significant morbidity and/or mortality in humans;

And, in addition

- Likely to pose a severe threat to public health, the capacity of public health systems to function, or national security.

Recommendation 2. Remove current blanket exclusions for research activities associated with surveillance and vaccine development or production. However, include and implement processes and procedures for urgent federal department level review and evaluation of ePPP research critical for public health or national security.

Recommendation 3.

Recommendation 3.1 Amend the USG P3CO framework to include and articulate specific roles, responsibilities, and expectations for investigators and institutions in the identification, review, and evaluation of research for potential involvement of ePPPs, taking into account existing review and oversight processes.

Recommendation 3.2. Local, institutional compliance procedures must be better harmonized, strengthened where needed, and adequate technical and financial assistance provided.

Recommendation 3.3. Designate a USG office with adequate technical and financial support to assist investigators and institutions in the review process to ensure consistent evaluation of PPP status.

Recommendation 4.

Recommendation 4.1 Amend the OSTP P3CO Policy Guidance to be consistent with the Belmont Report[6] and amend the HHS P3CO Framework to clarify that the seven categories of research outlined must be given extra care and considered throughout the life of the research, including the proposal, review, evaluation, and ongoing oversight process. In addition, develop principles and guidelines that can be applied and implemented to ensure, 1) there are no feasible alternative methods of obtaining the relevant benefits from proposed research that poses less risk; and 2) unnecessary risks have been eliminated and the remaining risks are justified by the potential benefits.

Recommendation 4.2 Develop an implementation directive/plan, additional guidance, educational materials, and standard operating procedures, including ongoing review, evaluation, and oversight procedures and criteria that can be used or adapted by funding institutions, research institutions, and investigators when implementing the policy.

Recommendation 5. Take additional steps to increase transparency in the review process at the federal and local levels, including sharing a summary of key determinants that informed ePPP research funding decisions.

Recommendation 6. Consider development of analogous policies and processes for identification, review, evaluation, and ongoing oversight of relevant research involving enhanced pathogens likely to pose severe threats to human health, food security, economic security, or national security by its impacts on animals or plants or to animal or plant products.

Recommendation 7. The conduct of ePPP research at international institutions receiving USG support for life sciences research, either directly or indirectly (e.g., via subawards or contracts), must also be subject to review, evaluation, and ongoing oversight procedures that are equivalent to domestic U.S. policies and procedures.

Phase 2 Recommendations

Recommendation 8.

Recommendation 8.1. Continue to facilitate sharing of experiences and best practices regarding DURC policy implementation.

Recommendation 8.2. Any updates to USG DURC policies, particularly updates regarding the scope of research subject to review and/or the relevant entities to which the policies apply,

[6] *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, articulates ethical principles and guidelines that served as the template for U.S. regulations governing research involving human subjects.

must involve relevant stakeholders and be accompanied by robust USG outreach and education and an adequate implementation period.

Recommendation 9. Remove the term "directly misapplied" from the DURC definition, which may not be beneficial to, and could potentially limit the identification and oversight of research that may pose significant threats, whether deliberate or accidental in nature.

Recommendation 10.

Recommendation 10.1. Expand the scope of research requiring review for potential DURC to include research that directly involves any human, animal, or plant pathogen, toxin, or agent that is reasonably anticipated to result in one or more of the seven experimental effects (Box 2).

Recommendation 10.2. Establish mechanisms and processes to ensure that investigators and institutions are executing their responsibilities effectively.

Recommendation 10.3. Review of bioinformatics, modeling, and other in silico experimental approaches and research involving genes from or encoding pathogens, toxins, or other agents for potential DURC is not recommended at this time. However, investigators and institutions should be aware of the potential risks of such research and continued assessment of the risks and benefits associated with advances and applications of such approaches must inform the ongoing evaluation of the scope of these policies.

Recommendation 11. Engage relevant stakeholder and publishing groups to encourage development and adoption of more uniform editorial policies, review processes, and best practices for identifying material that may raise significant biosecurity and biosafety concerns and facilitate the sharing of best practices and guidelines for assessing options for mitigating risks.

Recommendation 12. In line with the NSABB's 2016 recommendation regarding ePPP research, promote and ensure that all research meeting the scope of these policy frameworks conducted within the U.S. and/or supported by the U.S. government be subject to equivalent oversight regardless of funding source.

Recommendation 13. Develop an integrated approach to oversight of research that raises significant biosafety and biosecurity concerns, including ePPP research and DURC. Clearly articulate federal, institutional, and investigator responsibilities in the assessment and identification of proposed and ongoing research, and minimize the potential for duplicative or parallel institutional or federal review processes.

1. Introduction

Life sciences research involving pathogens serves a critical role in pandemic preparedness and ensuring that the United States and the global community are prepared to rapidly detect, respond to, and recover from biological threats, whether naturally occurring, accidental, or deliberate in origin.

Disease outbreaks over the past two decades caused by pathogens like SARS-CoV-1 and SARS-CoV-2, avian influenza, mpox virus, Ebola viruses, and others, underscore that the threats posed by infectious agents are not theoretical and that the disruptive impacts on public health and safety, animals, plants, agriculture, the environment, and economic and national security can be severe.

However, biosafety and biosecurity risks associated with undertaking research involving pathogens include the possibility of laboratory accidents and the deliberate misuse of the information or products generated. In particular, research having the potential to enhance the ability of pathogens to cause harm has elicited concerns and policy action. Such research may help define the fundamental nature of human-pathogen interactions, thereby enabling assessment of the pandemic potential of emerging infectious agents, informing public health and preparedness efforts, and furthering medical countermeasure development. It is of vital importance that the risks of such research be properly assessed and appropriately mitigated and that the anticipated scientific and social benefits of such research is sufficient to justify any remaining risks.

Advances in biotechnology, as well as convergence of life sciences with, and application of, other scientific disciplines such as engineering and computational sciences are developing rapidly. The developments hold tremendous promise for generating solutions to some of the most complex challenges we face, including groundbreaking advances in public and environmental health, energy and food security, and economic improvements. Additionally, the existence of these technological capabilities creates a moral obligation to act to achieve this promise when needed. However, these same advances also necessitate ongoing awareness and consideration of the evolving risk/benefit landscape. Currently, there are relatively low costs and easily accessible tools and techniques that can be applied to modify or generate beneficial and harmful agents. There has also been an increase in basic and clinical research involving high-consequence pathogens and differences in global capacities and systems to prevent, respond to, and mitigate the effects of biological incidents. These factors together contribute to increased recognition of the critical need for effective biosecurity and biosafety oversight policies and practices.

The United States has established a biosafety, biocontainment, and biosecurity oversight system[7] designed to protect laboratory workers, public health, agriculture, the environment, and national security. This system rests on a foundation of federal regulations, guidelines, and policies that differ in their scopes and specific purposes but are aimed collectively at ensuring that risks are identified, assessed, and appropriately mitigated.

Periodic reassessment of our oversight frameworks is necessary to ensure that they effectively address existing and emerging safety and security concerns while continuing to support scientific progress and a vibrant, innovative research enterprise.

To achieve this, the U.S. Government (USG) has undertaken a number of high-priority initiatives, including those contained in the National Biodefense Strategy and Implementation Plan for Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health

[7] https://www.phe.gov/s3/Documents/FESAP-guiding-principles.pdf

Security (NBS) (2022)[8]. The NBS outlines a single coordinated effort to orchestrate the full range of activities carried out across the USG to protect the American people and the nation's global interests from biological threats. Strengthening biosafety and biosecurity practices and oversight, reducing biological risks, and preventing the misuse of science and technology while promoting legitimate use and innovation, are core elements of the NBS and priority issues for the U.S. towards improving domestic and global health security. This commitment is exemplified by a number of activities, including the:

- National Security Memorandum on Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security[9],
- World Health Organization's Global guidance framework for the responsible use of the life sciences[10], and
- World Health Organization's Intergovernmental Negotiating Body[11] efforts to draft and negotiate a convention, agreement, or other international instrument to strengthen pandemic prevention, preparedness and response.

Current U.S. Oversight of Dual Use Research of Concern

Despite the tremendous value and benefits of life science research to public health and safety, certain types of research conducted for legitimate purposes can be utilized for both benevolent and harmful purposes. Dual use research of concern (DURC) is the subset of research defined as life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security.

Recognizing the importance of mitigating risks while ensuring that vital research is not unduly stymied, the USG issued two polices for the oversight of DURC. The United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern (2012)[12] requires regular federal review of federally supported research and requires federal agencies that fund or conduct life sciences research to identify DURC in their research portfolios and evaluate potential risks and benefits, and appropriately mitigate risks. The complementary United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern (released 2014, effective 2015)[13], applies to domestic institutions that receive federal funding for life sciences research and that also conduct research within the scope of the policy, even if the research itself is not supported by federal funds.

[8] https://www.whitehouse.gov/wp-content/uploads/2022/10/National-Biodefense-Strategy-and-Implementation-Plan-Final.pdf
[9] 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/
[10] https://www.who.int/publications/i/item/9789240056107
[11] https://inb.who.int/
[12] https://www.phe.gov/s3/dualuse/documents/us-policy-durc-032812.pdf
[13] https://www.phe.gov/s3/dualuse/documents/durc-policy.pdf

Foreign institutions that receive federal funds to conduct or sponsor research involving one or more of the 15 agents and toxins (Box 1) are also subject to the policy.

Research involving one or more of the agents or toxins that produces, aims to produce, or can be reasonably anticipated to produce one or more of the seven categories of experimental effects (Box 2) must be evaluated for potential DURC. The policies outline a framework for reviewing life science research to identify DURC and, if necessary, developing risk mitigation strategies to reduce potential risk of misuse. The goal of both policies is to preserve the benefits of life sciences research while minimizing the risk that the research could result in harm.

Box 1. DURC Policy Scope – Agents and toxins

Avian influenza virus (highly pathogenic)	Marburg virus
Bacillus anthracis	Reconstructed 1918 Influenza virus
Botulinum neurotoxin	Rinderpest virus
Burkholderia mallei	Toxin-producing strains of *Clostridium botulinum*
Burkholderia pseudomallei	Variola major virus
Ebola virus	Variola minor virus
Foot-and-mouth disease virus	*Yersinia pestis*
Francisella tularensis	

The possession, use, and transfer of any of these 15 agents and toxins are also regulated under federal law as Biological Select Agents and Toxins (BSAT)[14] by the Federal Select Agent Program (FSAP)[15]. The seven categories of experiments defined below are descriptors of research outcomes that may result in information, products, or technologies that warrant careful assessment for potential DURC.

[14] https://www.selectagents.gov/sat/list.htm?CDC_AA_refVal=https%3A%2F%2Fwww.selectagents.gov%2FSelectAgentsandToxinsList.html

[15] https://www.selectagents.gov/

Box 2. DURC Policy Scope – Categories of experiments

1. Enhance the harmful consequences of the agent or toxin;
2. Disrupt immunity or the effectiveness of an immunization against the agent or toxin without clinical or agricultural justification;
3. Confer to the agent or toxin resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates their ability to evade detection methodologies;
4. Increase the stability, transmissibility, or the ability to disseminate the agent or toxin;
5. Alter the host range or tropism of the agent or toxin;
6. Enhance the susceptibility of a host population to the agent or toxin; or
7. Generate or reconstitute an eradicated or extinct agent or toxin listed in the policy.

DURC oversight requirements do not apply to research involving attenuated or inactive forms of the agents and toxins that are excluded from oversight as select agents by the FSAP. The scope also does not include use of the genes from any of the listed agents, *in silico* experiments (e.g., modeling and bioinformatics approaches), or research related to the public, animal, or agricultural health impact of any of the listed agents such as modeling the effects of a toxin.

Key aspects of the DURC oversight framework, including the scope and roles and responsibilities articulated in the policies, were informed by findings and recommendations conveyed in the National Science Advisory Board for Biosecurity (NSABB) 2007 report *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information*[16] and by stakeholder input at NSABB meetings, public consultations, and in response to a USG request for comments via the Federal Register[17].

Oversight of Research involving Enhanced Potential Pandemic Pathogens

As part of continued prioritization of biosafety and biosecurity and in the context of debates regarding certain types of research, in 2014 through the *U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses*[18], the USG undertook a deliberative process to carefully examine the risks and benefits associated with certain gain-of-function (GOF) studies. During this deliberative process, U.S. government departments and agencies paused the release of federal funding for research that enhanced the pathogenicity or transmissibility of influenza, MERS, or SARS viruses among mammals by respiratory droplets.

[16] https://osp.od.nih.gov/wp-content/uploads/Proposed-Oversight-Framework-for-Dual-Use-Research.pdf
[17] https://www.federalregister.gov/documents/2013/02/22/2013-04127/united-states-government-policy-for-institutional-oversight-of-life-sciences-dual-use-research-of
[18] https://www.phe.gov/s3/dualuse/Documents/gain-of-function.pdf

The USG tasked the NSABB with making recommendation on this topic. The deliberative process engaged the NSABB and the National Academies of Sciences, Engineering, and Medicine (NASEM), which was tasked with facilitating broad public discussion on relevant issues to inform NSABB recommendations. The NSABB recommendations were issued in a 2016 report entitled *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research*[19]. In this report, the NSABB found that only a small subset of GOF research entails risks that are significant enough to warrant oversight; that in addition to the scientific merit of a study, legal, ethical, public health, and societal values should be taken into account; and that management of this small subset of research requires both federal and institutional oversight, awareness and compliance, and a commitment by all stakeholders to safety and security. Among the NSABB's recommendations were that this small subset of research receive an additional, multidisciplinary review before determining whether the research is acceptable for funding and that, if funded, such projects should be subject to ongoing oversight at the federal and institutional levels. The NSABB also described attributes of a pathogen resulting from such research, and principles that should guide funding decisions.

Aligned with the approach recommended by the 2016 NSABB report, the White House Office of Science and Technology Policy (OSTP) issued the *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)* (OSTP P3CO Policy Guidance) in January 2017[20]. The OSTP P3CO Policy Guidance provided federal departments and agencies with requirements for reviewing proposed research that is reasonably anticipated to create, transfer, or use potential pandemic pathogens (PPP) resulting from the enhancement of a pathogen's transmissibility or virulence in humans. Such a pathogen defines an enhanced PPP (ePPP). The OSTP P3CO Policy Guidance defines a PPP as a pathogen that satisfies both of the following characteristics:

- It is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations, and
- It is likely highly virulent and likely to cause significant morbidity and/or mortality in humans.

Adoption by federal departments and agencies of a review mechanism consistent with the provisions in the OSTP P3CO Policy Guidance satisfied requirements for lifting the research funding pause.

In response to, and in accordance with, the OSTP P3CO Policy Guidance, the Department of Health and Human Services released the *Department of Health and Human Services (HHS) Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens* (HHS P3CO Framework) in December 2017[21]. The HHS P3CO Framework describes a robust multidisciplinary, pre-funding review process that considers the potential scientific and public health benefits, biosafety and biosecurity risks, and appropriate risk mitigation strategies to help inform

[19] https://osp.od.nih.gov/wp-content/uploads/2016/06/NSABB_Final_Report_Recommendations_Evaluation_Oversight_Proposed_Gain_of_Function_Research.pdf
[20] https://www.phe.gov/s3/dualuse/documents/p3co-finalguidancestatement.pdf
[21] https://www.phe.gov/s3/dualuse/Documents/P3CO.pdf

agency decisions. The HHS P3CO Framework is intended to guide HHS funding decisions on proposed research that is reasonably anticipated to create, transfer, or use an ePPP, and seeks to preserve the benefits of life sciences research involving ePPPs while minimizing potential biosafety and biosecurity risks. ePPPs do not include naturally occurring pathogens that are circulating in or have been recovered from nature, regardless of their pandemic potential.

See Appendix A for current key roles and responsibilities for investigators, research institutions, federal departments and agencies, and the USG for the oversight of DURC and ePPP research.

2. NSABB Charge

The National Science Advisory Board for Biosecurity (NSABB)[22] is a federal advisory committee that addresses issues related to biosecurity and dual use research at the request of the USG. NSABB deliberations and recommendations have substantively informed current USG biosecurity policy frameworks, including policies for the oversight of DURC and P3CO.

In January 2020, the NSABB was issued a charge to provide recommendations on balancing security and public transparency when sharing information about research involving PPPs with enhanced transmissibility or virulence in humans and to evaluate and analyze the USG DURC policies. However, due to the rapid escalation of the COVID-19 pandemic, the work of the Board on this charge was deferred to allow members of the NSABB to prioritize public health, research, and response activities.

In February 2022, HHS reconvened the NSABB and issued a revised charge to evaluate and provide recommendations on the effectiveness of the current oversight frameworks for research involving ePPPs and DURC. The NSABB's charge was divided into two phases as outlined below.

Phase 1 – P3CO Policy Review and Evaluation

"The NSABB will evaluate and provide recommendations to the Office of Science and Technology Policy (OSTP) and the Department of Health and Human Services (HHS) on the effectiveness of the current oversight framework for research involving enhanced potential pandemic pathogens (ePPPs). In developing these recommendations, the NSABB should consider the OSTP *Recommended Policy Guidance for Departmental Development of Review Mechanism for Potential Pandemic Pathogen Care and Oversight*[23] and the process adopted by HHS for the review and oversight of proposed research involving enhanced potential pandemic pathogens. Review should include:

A. Policy scope, in terms of preserving benefits of ePPP research while minimizing potential biosafety and biosecurity risks, including whether wild type pathogens, animal models of transmissibility, etc., should be considered;
B. Considerations for supporting ePPP research internationally, per OSTP framework encouraging harmonized policy guidance; and

[22] https://osp.od.nih.gov/policies/national-science-advisory-board-for-biosecurity-nsabb#tab0/
[23] https://www.phe.gov/s3/dualuse/Documents/P3CO-FinalGuidanceStatement.pdf

C. Balancing considerations regarding security and public transparency when sharing information about research involving ePPPs.

The review should consider the impact that the Policy Guidance has had on work involving the creation, transfer, or use of enhanced potential pandemic pathogens, research programs, and institutions when developing these recommendations."

Phase 2 – DURC Policy Review and Evaluation

"The Office of Science and Technology Policy (OSTP) and the National Security Council (NSC) formally request the National Science Advisory Board for Biosecurity (NSABB) evaluate, analyze, and provide specific recommendations on the following tasks and subtasks:

A. The U.S. Government DURC Policies, the *United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern* and the *United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern*, were released in 2012 and 2014 respectively, and require thorough review to inform future policy and governance deliberations. The NSABB should:

    1. Evaluate the effectiveness of the DURC Policies in achieving the issuances' intent; evaluate the impact on research institutions and the U.S. Government's ability to support research; and identify any challenges with implementation;
    2. Reevaluate the DURC definition, considering advances in life sciences research and convergence with other scientific disciplines and sectors;
    3. Evaluate the effectiveness of the DURC pathogen list and experimentation type construct to determine if the approach sufficiently addresses future potential threats, including across the spectrum of life sciences, is conducive to research risk-mitigation, and whether alternative approaches are warranted for consideration by the USG; and
    4. Evaluate the effectiveness of the DURC policies with regard to publication, public communication, and dissemination of dual-use research methodologies and results.

B. With the understanding that U.S. Government DURC Policies will undergo review in Phase 2A., and in accordance with Section 8 of the January 2017 *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)*, the NSABB should:

    1. Evaluate Section 8 of the *Policy Guidance for P3CO*, Future Commitments of the *P3CO Policy Guidance*, and provide recommendations on possible *P3CO Policy Guidance* incorporation into policy frameworks associated with any recommended revisions of the DURC Policies.

Throughout Phase 2, the NSABB should consider the need for flexible and adaptive governance approaches that 1) keep pace with scientific advances and the evolving understanding of risks and benefits; 2) can coalesce and integrate existing governance guidance or policy, 3) can be applied to mitigate risk not only from research of concern but other biosecurity and biosafety considerations."

To efficiently address its charge, the NSABB formed two Working Groups – the Working Group to Review and Evaluate Potential Pandemic Pathogen Care and Oversight (P3CO) Policy and the Working Group to Review and Evaluate Dual Use Research of Concern (DURC) Policies. To help inform the NSABB's deliberations and federal evaluation of these biosecurity policy frameworks, the National Institutes of Health (NIH) held two public engagement sessions in April and June 2022 to receive feedback and perspectives from stakeholders regarding their experiences with policy implementation, the effects of the policies in terms of achieving their stated goals, and possible alternative approaches for research oversight. The NSABB Working Groups also considered public comments and stakeholder perspectives shared as part of the NIH-hosted listening sessions and public NSABB meetings convened in 2020 and 2022.

3. Evaluation of Current DURC and P3CO Policy Frameworks

The 2012 and 2014 USG policies were designed to complement existing biosecurity policies and regulations regarding the possession and handling of certain high-consequence biological agents and material. Together, the policies outline clear roles and responsibilities of the key stakeholders in the research lifecycle including research investigators and institutions and federal funding agencies. Their central purpose was to establish and strengthen a shared system of review and oversight between the federal agencies and local institutions for the identification and oversight of a subset of life sciences research involving certain high-consequence pathogens and toxins to identify potential DURC. In so doing, the policies are designed to preserve the benefits of life sciences DURC while appropriately mitigating identified risks—in particular, knowledge, information, products, or technologies generated from such research that could be misused to cause harm. The overarching purpose of the USG P3CO framework is similar—to provide enhanced oversight of a subset of research deemed to entail risks that are potentially significant enough to warrant additional oversight to safely realize the benefits of the research. However, the two frameworks differ in their approaches to oversight, including specification of the respective scopes and the required roles and responsibilities of key stakeholders across the federal agencies and local institutions.

This circumscribed scope facilitated the introduction and adoption of what was, at the time, a new oversight paradigm in the life sciences and allowed the concentration of efforts and resources on reviewing the subset of research deemed to pose the highest potential for significant harm if the research was misused.

As an alternative to a list-based approach to oversight, P3CO employs an approach that requires additional review and oversight of any research that is reasonably anticipated to create, transfer, or use a PPP resulting from the enhancement of the transmissibility or virulence in humans of any pathogen (i.e., an enhanced PPP). In this aspect, the P3CO framework is more flexible than DURC policy and allows for the identification of potential ePPP research and mitigation of risks from a much broader swath of life sciences research despite also being focused on a specific subset of research, including with pathogens that may emerge in the future. However, the absence of a list circumscribing the oversight scope similar to the approach applied in the DURC policies has the potential to introduce a degree of uncertainty as to what is covered.

Both the P3CO and DURC current oversight frameworks apply to federally funded research conducted at or sponsored by institutions within and outside the U.S. However, the oversight of DURC applies additionally to non-federally funded research conducted at or sponsored by institutions based in the U.S. that receive federal funding for life sciences research, even if the research itself is not supported by USG funds. Under the institutional DURC policy, notification of the outcomes of institutional reviews for potential DURC is made to the relevant USG agency or office thus facilitating USG awareness of non-federally funded work at institutions subject to the policy.

The two DURC policies articulate specific roles and responsibilities of the USG, federal funding agencies, research investigators, institutions, and institutional review committees in the identification and oversight of DURC. Their complementarity recognizes the importance of oversight by federal funders of life sciences research and by institutions and investigators, who are the most familiar with the research conducted in their facilities.

The DURC policy framework further outlines time parameters for various steps in the review process—information that helps set expectations for investigators, institutions, and funding agencies, and facilitates coordination of DURC oversight with scientific, budgetary, and other research administration processes. Importantly, the 1-year implementation period granted under the institutional DURC policy facilitated the education and training of staff and opportunities to share approaches taken to establish institutional oversight systems and discuss associated challenges and solutions.

The OSTP P3CO Policy Guidance and corresponding HHS P3CO Framework provide federal departments and agencies with requirements for reviewing proposed research, specifically, the identification of research reasonably anticipated to create, transfer, or use a PPP resulting from the enhancement of the transmissibility or virulence in humans of any pathogen (i.e., an ePPP), however, analogous review requirements for institutions and investigators are not provided in the P3CO framework. Furthermore, the P3CO framework does not include time parameters for the review process. In this aspect, the DURC policies provide for a more comprehensive review than the P3CO frameworks, and involve the institutions and investigators that are well positioned to identify, oversee, and communicate research on a continuous basis.

4. Departmental Review of Research Under P3CO Framework

To date, in accordance with the HHS P3CO Framework, three projects have been referred by funding agencies to the Department of Health and Human Services for evaluation. All three projects were evaluated through the NIH peer-review process and found to be scientifically meritorious before referral for departmental review. For two projects, the HHS P3CO Review Group determined that the research was acceptable for HHS funding with recommended changes to increase the potential benefits while decreasing risks. The funding agency incorporated the recommended changes into terms and conditions that were placed on the awards. For the third project, the HHS P3CO Review Group determined that a subset of the proposed research was acceptable for funding with the implementation of additional risk mitigation measures. The funding agency ultimately decided to redirect all funds under the award to support alternative approaches that do not involve a potential pandemic pathogen resulting from the enhancement of a pathogen's transmissibility or virulence in

humans. Information about these reviews and outcomes is available on the Science Safety Security website[24].

5. NSABB Working Group Draft Findings and Recommendations to the U. S. Government

In developing draft findings and recommendations, NSABB Working Groups reviewed relevant policies and guidance and prior NSABB and NASEM reports. NSABB Working Groups also consulted with subject matter experts in pathogen research, research administration and oversight, biosafety and biosecurity, biodefense, and national security, among others from the USG, federal funding agencies, academic institutions, and scientific and professional societies, and considered public comments. The Working Groups received and considered varying perspectives regarding the scope of research that should be addressed by the policies, the roles and responsibilities of stakeholders, appropriate balance of public transparency and security, and the potential impacts on research programs and the scientific workforce of uneven oversight requirements and undue burden.

Some subject matter experts suggested that the negative stigma associated with certain research may discourage the conduct of potentially vital work and discourage young scientists from pursuing training and research careers in critical areas. Consideration was also given to domestic and international oversight differences and the possibility of such research and researchers moving to other countries due to undue delays, increased burdens, and perceptions of a lack of domestic support.

6. NSABB Working Group Findings on P3CO & DURC Oversight Frameworks

Phase 1 Findings

Policy scope and definitions

Finding 1. Potential pandemic pathogen (PPP) and enhanced PPP (ePPP) definitions. USG P3CO policy requires additional federal department-level review of proposed research that is reasonably anticipated to involve the creation, transfer, or use of ePPPs—defined as a PPP resulting from the enhancement of a pathogen's transmissibility and/or virulence. While the starting pathogen does not have a be a PPP, the term "enhanced PPP" could suggest otherwise and may contribute to a lack of clarity regarding what research is subject to additional federal department-level review under the P3CO Framework. In particular, research involving the enhancement of pathogens that do not meet the PPP definition (e.g., those with low or moderate virulence) but is anticipated to result in the creation of a pathogen with the characteristics described by the PPP definition could be overlooked. Such a modified pathogen could pose a severe threat to public health, the capacity of public health and healthcare systems to function, or national security.

Finding 2. Exclusions and urgent review. The identification of ePPP research is informed by the current body of scientific evidence and knowledge and necessarily entails some degree of uncertainty. It is therefore important when proposed or ongoing research with potential ePPP is identified that reviews and evaluations of PPP status, whether at institutional or federal levels, be made in light of current scientific knowledge and updated in response to new findings and knowledge. The review, evaluation,

[24] https://www.phe.gov/s3/dualuse/Pages/ResearchReview-PPP.aspx

and ongoing oversight system must be consistent and clearly articulated across the continuum from institutions to federal funding agencies, and when additional review is required at the federal department level. The focus for such assessments must be on the potential for an activity or a modification to involve or produce a pathogen that meets the criteria for an ePPP and not on the context in which this activity or modification is carried out.

All research activity that is reasonably anticipated to involve the creation, transfer, or use of ePPPs must be subject to the additional review under the U.S. Government (USG) P3CO framework. However, the often-critical contributions that surveillance and vaccine development activities make to public health response are recognized and necessitate mechanisms to ensure that if ePPP research is identified and deemed critical to public health or national security, its review and evaluation under the USG P3CO policy must not be unduly delayed.

Policy and implementation

Finding 3. Enhanced institutional responsibility. Investigators and institutions are critical components of a comprehensive oversight system, as they are most familiar with the research proposed to be or being conducted in their facilities and are in the best positions to promote and strengthen responsible conduct and ensure ongoing biosafety and biosecurity controls. The current P3CO policy does not adequately incorporate the roles of investigators and institutions in the local development, review, and ongoing oversight of research.

Finding 4. P3CO policy and implementation directives. The additional review process outlined under the OSTP Recommended Policy Guidance for Departmental Development Mechanisms for Potential Pandemic Pathogen Care and Oversight (OSTP P3CO Policy Guidance)[25] and HHS Framework for Guiding Funding Decisions of Proposed Research Involving Enhanced Potential Pandemic Pathogens (HHS P3CO Framework)[26] are generally appropriate as designed at the federal department level. However, Section III.3 and III.4 of the OSTP P3CO Policy Guidance regarding risks and benefits are inconsistent with similar policies as described in the Belmont Report[27]. Additionally, Section IV.C of the HHS P3CO Framework indicates that the extra care in reviewing proposed research which is reasonably anticipated to generate an outcome from one of the seven categories of research outlined in that section is only required at the HHS department level review.

An implementation directive for the P3CO Framework from HHS to HHS funding agencies is lacking. Directives and guidance from the federal funding agency for research institutions and principal investigators are also lacking. Both are needed to effectively implement the HHS P3CO Framework. The lack of an implementation directive and guidance has contributed to uncertainty, resulting in a lack of clarity regarding the timing and expected requirements of the review process, and potential opportunity costs associated with investigators being deterred from pursuing important research or careers specializing in certain pathogens. Additional education and guidance are needed to facilitate consistent and efficient implementation of the P3CO policy, including what is required in the systematic assessment of risks and benefits by all stakeholders. This is also required to enhance awareness and consideration of potential biosafety and biosecurity risks, and mitigation of such risks,

[25] https://www.phe.gov/s3/dualuse/documents/p3co-finalguidancestatement.pdf
[26] https://www.phe.gov/s3/dualuse/Documents/P3CO.pdf
[27] https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf

throughout the research life cycle, including during the development of research proposals and through an ongoing oversight basis until completion of the research.

Transparency and accountability

Finding 5. Review process transparency. Under the HHS P3CO Framework, proposed research identified by the funding agency as reasonably anticipated to create, transfer, or use ePPPs undergoes an additional multidisciplinary review by a federal department level review group. The review group constituted by HHS appears to have the appropriate expertise, and the process takes into account the need to protect potentially sensitive personal and proprietary information and facilitates open discussion of issues relevant to national security and public health preparedness within the federal department review group. However, increased transparency in the review process is needed. This would enable a greater understanding of and engender trust in the review and oversight processes for ePPP research.

Additional Working Group considerations

Finding 6. Animal and plant pathogens. The focus of the current HHS P3CO framework on pathogens that are likely to cause disease in humans is appropriate and covers funding agencies within HHS. However, certain research involving enhanced pathogens may pose significant threats to animal and plant health that are outside of HHS oversight authorities, and which could cause severe secondary impacts on human health, in addition to impacts on food security, economic security, and national security.

Finding 7. International ePPP research. Pathogens that pose pandemic threats can emerge anywhere in the world and spread rapidly. Global collaboration on international surveillance, biomedical research, and safe and secure sharing of data and samples are vital to U.S. pandemic preparedness and response, including the development of diagnostics, vaccines, and therapeutics, as well as broader global health security. Rigorous biosafety and biosecurity compliance and ongoing oversight are critical to realizing the shared benefits of research that may be anticipated to create, transfer, or use enhanced PPPs, however capacities and systems to do so currently vary. Support for international ePPP research by the U.S. should be coupled to review, evaluation, oversight, and compliance processes that are deemed to be equivalent to requirements that govern domestic research in the United States. On a broader level, renewed commitments to international engagement and efforts to harmonize and strengthen international biosafety and biosecurity best practices, norms, and standards are needed.

Phase 2 Findings

Policy scope and definitions

Finding 8. Effectiveness of DURC oversight framework. Based on feedback shared by groups including research investigators, administrators, and program staff from academic institutions and federal funding agencies, including during USG-hosted stakeholder engagement meetings, the DURC policies appear to have achieved the original intent to establish and strengthen a shared system of review and oversight between the federal and local institutional levels for the identification and oversight of a subset of life sciences research involving certain high-consequence pathogens and toxins in order to identify DURC and mitigate potential risks. Implementation of what was at the time a new process for biosecurity oversight of life sciences research, was facilitated in part by a well-defined and circumscribed policy scope. However, the policy scope limits the evaluation of the framework's success

to only a small fraction of the life sciences research enterprise, i.e., research conducted or sponsored by federally funded institutions that involves one or more of the 15 listed agents and toxins. An expansion of the policy scope (beyond the 15 agents/toxins) will facilitate appropriate review of additional research with the potential to raise biosecurity concerns, enhance awareness of dual use issues among the broader life sciences research community, and contribute to a research enterprise grounded in a culture of responsible design, conduct, evaluation, and communication of research.

When the DURC policies were introduced, the roles and responsibilities of key stakeholders including the USG, federal funding agencies, research institutions, and investigators, were clearly articulated. In addition, the USG developed and disseminated education and training material and guidance to aid implementation. This included the DURC Companion Guide. Stakeholders emphasized the importance of this guidance to enable effective implementation. The USG also conducted significant stakeholder engagement to raise awareness of the dual use issue prior to and during policy development and ongoing guidance regarding implementation, which contributed to the policy framework achieving the intent. These efforts, along with the flexibility afforded by the policies regarding the establishment of review and oversight processes, as well as the one-year implementation period provided for the 2014 institutional DURC policy, served to mitigate some of the challenges associated with policy implementation.

The review and oversight of DURC could require substantial time, personnel, expertise, and other resources. However, federal and non-federal stakeholders shared that they have largely found policy implementation manageable and have been able to successfully execute their responsibilities. The resources needed to do so are generally commensurate with the size of research portfolios subject to the policy. Federal funding agencies and institutions with large pathogen research portfolios are perhaps the most affected but, factoring in the current scope, have been able to scale resources and limit any negative impacts on the ability to support vital research.

Finding 9. Definition of DURC. The DURC definition articulated in the 2012 and 2014 USG policies was carefully crafted in large part to focus identification and risk mitigation efforts and resources on a subset of research involving a specific list of agents that could be reasonably anticipated to generate knowledge, information, or products that could cause significant harm if deliberately misused. This policy was in addition to other biosafety and biosecurity guidelines, policies, and regulations focused on mitigating risks associated with research conduct and the possession, transfer, and use of the agents or toxins. However, this definition fails to address the potential for significant threats that are not solely associated with deliberate misuse.

A determination regarding whether research meets the definition of DURC requires a risk assessment that carefully considers potential dual use risks. Such assessments are based on the best available information at the time but necessarily entail a degree of uncertainty that can vary but cannot be eliminated. This includes uncertainties and unknowns regarding the identities and potential motivation or intent of nefarious actors. Advances in biotechnologies and convergence of life sciences with other scientific disciplines continue to provide tremendous benefits but simultaneously alter the risk landscape associated with research involving pathogens, which add to the challenge of assessing dual use risks.

Finding 10. DURC policy scope. The current scope of the DURC policies is limited to a well-defined subset of life sciences research that directly involves one or more of 15 listed agents/toxins and seven categories of experiments. Such a list-based approach to oversight is inherently less adaptive compared to other approaches. The list of agents/toxins is restricted to a fraction of those that are regulated as BSAT, and which have been determined to have the potential to pose a severe threat to public health and safety, to animal and plant health, or to animal or plant products. A risk-based approach or more encompassing scope is more appropriate to address existing and potential future threats of research of concern, including those associated with misapplication of advances in biotechnologies and the convergence of the life sciences with other scientific disciplines.

The 2012 and 2014 DURC policies established governmental and institutional oversight of DURC respectively. These policies are complementary and comprise a shared system of oversight. Per these DURC policies, both federal funding agencies and research institutions subject to the DURC policies are required to review their research portfolios to identify DURC. Some research institutions have voluntarily chosen to expand the scope of research they review for potential DURC to include the entirety of their pathogen research portfolios. However, it is acknowledged that requiring the implementation of DURC review processes to evaluate all research involving any human, animal, or plant pathogen, toxin or other agent may result in additional burden to both research institutions and federal funding agencies. The magnitude of this additional burden will vary based on the nature and size of an institution's or funding agency's pathogen research portfolio.

Bioinformatics, modeling, and other *in silico* experimental approaches, as well as the use of genes from pathogens, have the potential to provide knowledge, information, products, or technologies that could be misused to cause harm and have been cited as a potential gap in current DURC oversight. However, in silico approaches usually require in vitro, in vivo, or other real-world experimentation, validation and/or expression of a gene product, which in many circumstances would fall under the recommended oversight framework.

Finding 11. Responsible communication of research. Responsible communication of research methods and results is a central component of mitigating risks associated with this subset of research. Most of the research subject to the current DURC policies is fundamental research and the findings are intended to, and can be, communicated responsibly if risks are identified early in the research life cycle and adequate consideration is given to the timing, modes, and venues of communication, among other risk mitigation measures. There are significant challenges to managing DURC at the publication stage. Approaches and mechanisms for rapidly disseminating life sciences research methods and results continue to evolve. The use of preprint servers, social media, and other digital platforms in the life sciences continues to grow. The DURC policies do not currently articulate required roles and responsibilities for scientific journals or publishers, however numerous journals and publishers have developed policies and/or procedures for the review and identification of DURC and other security risks in manuscripts being considered for publication.

Finding 12. Enhanced oversight of non-federally funded research. A substantial percentage of U.S. biotechnology research and development is supported by non-federal funding. Certain non-federally funded research involving pathogens is subject to required federal oversight. Additionally, there is significant precedent for the voluntary adoption of biosafety and biosecurity guidance and best

practices by the private sector. However, the potential biosafety and biosecurity risks associated with DURC and ePPP research justify USG efforts to introduce oversight via mechanisms that would enable oversight of all relevant research activities, regardless of the funding source. Such oversight would help to enhance federal awareness of relevant research and promote a national culture of responsibility in research.

Finding 13. Incorporation of ePPP research and DURC oversight. Research involving ePPP can include both biosafety and biosecurity risks and the potential that the knowledge or products derived from ePPP research could be misapplied to cause harm or have unintentional, but harmful consequences. There are substantive overlaps between the DURC and ePPP research oversight frameworks, including the overarching intents, as well as the entities involved in policy implementation. However, current differences between the frameworks, including the timing of the initial assessments and the lack of clear roles for investigators and institutions in the identification of potential ePPP research need to be reconciled. Recommended changes to include pathogens, toxins, and other agents in the DURC policy scope facilitate incorporation of ePPP research oversight. However, it is important that specific principles identified for the oversight of ePPP research be included in a proposed harmonization with DURC safeguards and that review and oversight processes, as well as risk mitigation measures, be commensurate with the degree of potential risk posed.

NSABB Working Group Recommendations on P3CO & DURC Oversight Frameworks

Phase 1 Recommendations

Recommendation 1. Amend USG P3CO policy to clarify that federal department-level review is required for research that is reasonably anticipated to enhance the transmissibility and/or virulence of any pathogen (i.e., PPPs and non-PPPs) if the resulting pathogen is reasonably anticipated to exhibit the following characteristics that meet the definition of a PPP:

- Likely moderately or highly transmissible and likely capable of wide and uncontrollable spread in human populations; and/or
- Likely moderately or highly virulent and likely to cause significant morbidity and/or mortality in humans;

And, in addition

- Likely to pose a severe threat to public health, the capacity of public health systems to function, or national security.

Assessments for the identification of ePPP research must be focused on the potential for an activity or a modification to involve or produce a pathogen that meets the criteria for an ePPP and not on the specific experimental approach or method to be undertaken. However, research reasonably anticipated to involve any of the experimental categories described in Section IV.C of the current P3CO Framework warrants careful evaluation for its potential to produce an ePPP. An amended P3CO policy must also provide implementing directives, instructions and guidance on how to apply the experimental categories identified in Section IV. C of the current P3CO Framework to help illustrate how modifications to a pathogen would or would not cross the threshold necessary to constitute ePPP research.

Recommendation 2. Amend the USG P3CO policy to reconsider current exclusions for research activities associated with surveillance and vaccine development or production, which could be broadly interpreted as blanket exclusions that are not warranted. The identification, review, and evaluation of potential ePPP research considers risks and benefits, including whether the research is critical to public health or national security, thus these exclusions are not needed.

In parallel, implement processes and procedures for urgent federal department level review and evaluation of ePPP research critical for public health or national security as determined by the appropriate authority.

Recommendation 3.

Recommendation 3.1 Amend the USG P3CO framework to include and articulate the specific roles, responsibilities, and expectations for investigators and institutions in the identification, review, and evaluation of research for potential involvement of ePPPs, taking into account existing review and oversight processes. This includes responsibilities to notify relevant institutional and funding agency officials of any new or unanticipated results from ongoing research that could potentially alter an assessment of whether the research is reasonably anticipated to involve an ePPP.

Recommendation 3.2 Local, institutional compliance procedures must be better harmonized, strengthened where needed, and adequate technical and financial assistance provided.

Recommendation 3.3 A USG office with adequate technical and financial support must be designated to assist investigators and institutions in the review process to reliably identify proposed and ongoing research for potential involvement of ePPPs to ensure consistent evaluation of PPP status.

Recommendation 4. P3CO framework.

Recommendation 4.1 Amend Section III.3 and III.4 of the OSTP P3CO Policy Guidance to be consistent with the Belmont Report. For example, amend Section III.3 to, “There are no feasible, scientifically sound alternative ways of obtaining the benefits sought in the research in a matter that poses less risk”. Amend Section III.4 to, “Risks that are not necessary to answer an important scientific question have been eliminated and an overall assessment of remaining risks finds that they are justified by the potential benefits to society from the research.”

Amend Section IV.C. of the HHS P3CO Framework to clarify that the seven categories of research outlined in this section must be given extra care and considered throughout the research proposal, review, evaluation, and ongoing oversight process by principal investigators, institutions, and federal funding agencies (including those outside HHS) in addition to the federal department-level review.

Recommendation 4.2 Implementation directives. The USG must dedicate resources and personnel to the development of an implementation directive/plan, additional guidance, educational materials, and standard operating procedures, including ongoing review, evaluation, and oversight procedures and criteria that can be used or adapted by funding

institutions, research institutions, and investigators when implementing the policy. The companion guide[28] and other material developed to aid implementation of the USG dual use research of concern (DURC) policies may serve as a starting model. An implementation plan must outline clear roles and responsibilities for investigators, institutions, federal funding agencies, and federal departments. Guidance and education material must include, but not limited to the following:

- Steps, considerations, and criteria for the identification, iterative review, and evaluation of PPP status based on results of the review, as well as ongoing oversight of potential ePPP research
- Directives and guidance on how to apply the seven experimental categories in Section IV. C of the current HHS P3CO Framework to illustrate how modifications to a pathogen would or would not cross the threshold necessary to constitute a PPP that is likely to pose a severe threat to public health, the capacity of health systems to function, or national security
- Types of questions and information considered at each stage of the review process
- Systematic assessment of risks and benefits that includes types of risks and benefits assessed (risks should include consideration of short and long-term risks and potential consequences)
- The expected components of material evaluated (e.g., risk/benefit analysis, risk mitigation plan, etc.)
- Substantive information on biosafety and biosecurity standards, controls, and safeguards
- Standards for review timelines under emergency and non-emergency conditions
- Expectations and standards for responsible communication of research

In addition, the USG must develop principles and guidelines that can be applied and implemented to ensure, 1) there are no feasible, scientifically sound alternative methods of obtaining the relevant benefits from the proposed research in a manner that poses less risk; and 2) unnecessary risks have been eliminated and an overall assessment of remaining risks finds that they are justified by the potential benefits to society from the research.

Recommendation 5. The USG must take additional steps to increase transparency in the review process at the federal and local levels. This would in part be accomplished by development and release of an implementation directive, plans, and guidance (see recommendation 4), but the USG must also share a summary of key determinants that informed ePPP research funding decisions based on results of the additional USG federal department level review and evaluation process.

Recommendation 6. National Security Memorandum-16 (NSM-16)[29] went into effect on November 10, 2022, replacing HSPD-9 - Defense of U.S. Agriculture and Food[30]. When implementing NSM-16, the USG must consider development of analogous policies and processes for identification, review, evaluation, and ongoing oversight of relevant research involving enhanced pathogens that requires additional federal department level review likely to pose severe threats to human health, food

[28] https://www.phe.gov/s3/dualuse/documents/durc-companion-guide.pdf
[29] https://www.whitehouse.gov/briefing-room/presidential-actions/2022/11/10/national-security-memorandum-on-on-strengthening-the-security-and-resilience-of-united-states-food-and-agriculture/
[30] https://www.aphis.usda.gov/animal_health/emergency_management/downloads/hspd-9.pdf

security, economic security, or national security by its impacts on animals or plants or to animal or plant products.

Recommendation 7. The conduct of ePPP research at international institutions receiving USG support for life sciences research, either directly or indirectly (e.g., via subawards or contracts), must be subject to review, evaluation, and ongoing oversight procedures that are equivalent to domestic U.S. policies and procedures. This must include U.S. review and oversight of safety and security measures, risk management practices, and assessment of applicable policies and procedures for comparability to relevant U.S. policies and procedures.

Commitments to international engagement and efforts to harmonize and strengthen international norms, standards, education, training related to the biosafety and biosecurity oversight of ePPP research must be renewed, leveraging existing bodies and fora (e.g., the World Health Organization, the Global Health Security Agenda, the Biological Weapons Convention, or relevant future treaties and other multilateral agreements).

Phase 2 Recommendations

Recommendation 8.

> **Recommendation 8.1** Continue to facilitate sharing of experiences and best practices regarding DURC policy implementation.
>
> **Recommendation 8.2** Any updates to USG DURC policies, particularly updates regarding the scope of research subject to review and/or the relevant entities to which the policies apply, must involve relevant stakeholders and be accompanied by robust USG outreach and education similar to when the policies were first introduced. An adequate implementation period, similar to that which accompanied release of the 2014 institutional DURC policy, must accompany any policy changes to allow affected stakeholders time to understand their roles and responsibilities and establish or adapt required oversight procedures and provide training to staff, and sufficient flexibility must be included to enable successful implementation across all these stakeholders. Adequate technical and financial assistance must be provided to institutions required to implement the policy. In addition to the development and provision of updated education and guidance material, a dedicated office with adequate technical and financial support must be designated to assist investigators and institutions with understanding and implementing the policy.

Recommendation 9. Remove the term “directly misapplied” from the DURC definition. The focus of the existing DURC policies is on the misuse of knowledge, information, or products of research, however the term “directly misapplied” could limit the identification of research of concern that may pose significant threats, whether deliberate, accidental or unintentional in nature. Risk assessments should acknowledge uncertainty but should not preclude reasonable consideration of whether and how near-term or rapid advances in biotechnology, or the convergence of life sciences with other scientific disciplines, may contribute to significant threats from research of concern.

Recommendation 10.

Recommendation 10.1. Expand the scope of research requiring review for potential DURC to include research that directly involves any human, animal, or plant pathogen, toxin, or agent and that is reasonably anticipated to result in one or more of the seven experimental effects (see Table 2).

Recommendation 10.2. The number of research projects that need to be assessed for potential involvement of one of the seven experimental effects could significantly increase, depending on the institution or investigator. To mitigate undue burden and potential delays to research review and approval process, the responsibility for assessing the applicability of the experimental effects should primarily rest with the investigator and institution who/which are most familiar with the research conducted in their facilities and are well positioned to identify, oversee, and communicate research of concern on a continuous basis. Federal funding agencies that support research involving human, animal, or plant pathogens, toxins, or agents should prioritize resources for the independent review of research identified by institutions as involving one or more of the experimental effects. Establishing mechanisms and processes will be necessary to help ensure that investigators and institutions are executing their responsibilities effectively. Potential mechanisms should include, but not be limited to, enhancing education and guidance material on the institutional identification of this research of concern, facilitating the exchange of best practices, and amending the forms and/or information requested when applying for federal funds.

Recommendation 10.3. Review of bioinformatics, modeling, and other *in silico* experimental approaches and research involving genes from or encoding pathogens, toxins, or other agents as part of the oversight framework described in this report is not recommended at this time, continued assessment of the risks and benefits associated with advances and applications of such approaches must inform future evaluations of the scope of these policies to help ensure that associated risks are appropriately identified and managed regardless of their origin.

Recommendation 11. Engage scientific societies, publishers, journal editors, and other relevant professional and expert stakeholder groups to encourage development and adoption of more uniform editorial policies, review processes, and best practices for identifying material that may raise significant biosecurity and biosafety concerns and facilitate the sharing of best practices and guidelines for assessing options for mitigating risks.

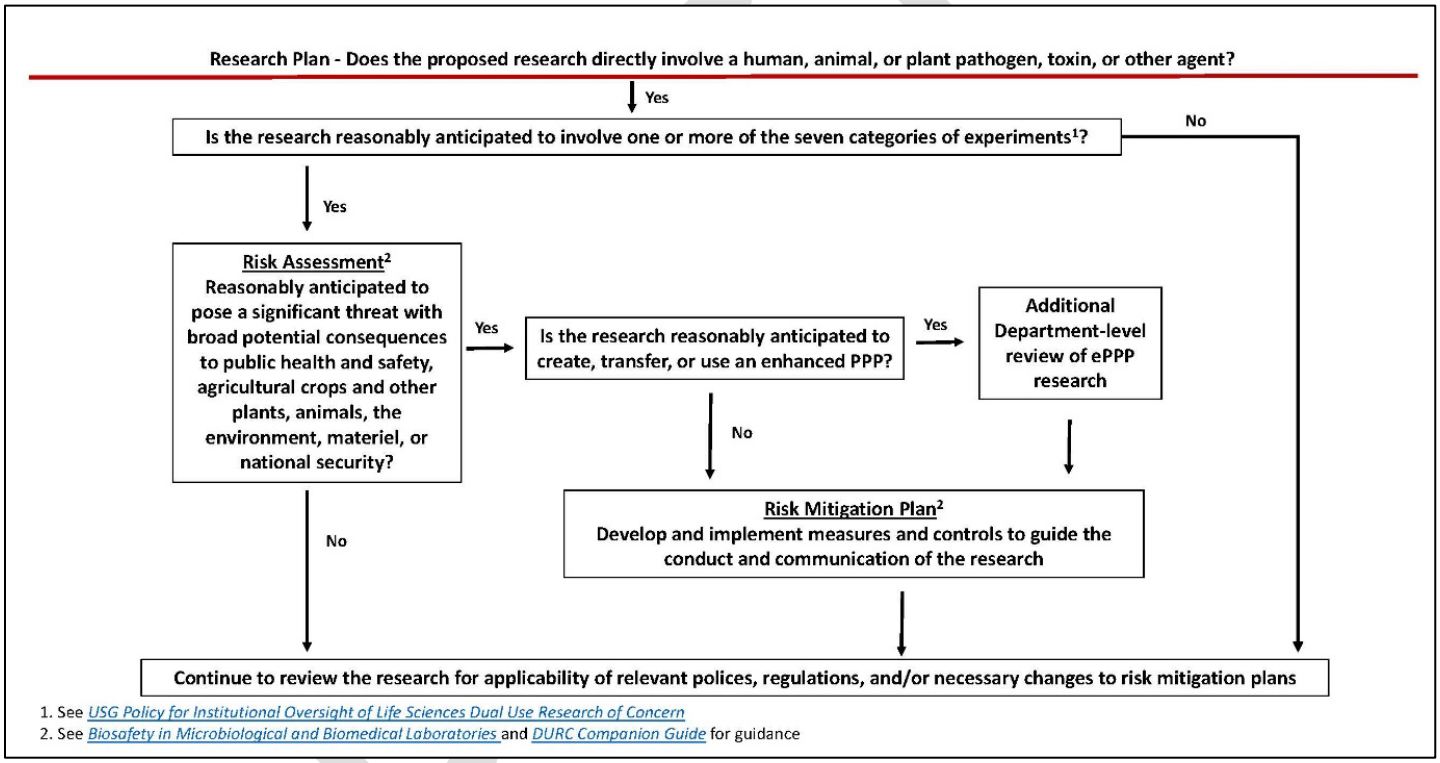
Recommendation 12. In line with the NSABB's 2016 recommendation regarding ePPP research, implement mechanisms to promote and ensure that all DURC and ePPP research conducted domestically or internationally by institutions supported by federal funding agencies, be subject to equivalent criteria to identify and mitigate the potential risks associated with DURC and ePPP research, regardless of funding source.

Recommendation 13. Clear roles and responsibilities for investigators and institutions must be developed for the identification, assessment, and appropriate notification of institutional and federal entities of proposed and ongoing research that raises significant biosafety and biosecurity concerns. This would include research that may warrant additional federal review for its potential to create, transfer, or use ePPPs. Figure 1 illustrates a conceptual approach for the identification and oversight of

research of concern described in this report, and that minimizes the potential for duplicative or parallel institutional or federal review processes.

Additionally, provide guidance to investigators and institutions for developing and submitting research proposals that may involve the types of research of concern discussed, including the information that would facilitate federal level reviews and development of risk mitigation plans. Applications for federal funding should include notification of whether the research is reasonably anticipated to produce any of the seven experimental effects, and if the proposed research may involve research of concern, as described in this report. Such research would need to be identified as having undergone appropriate institutional review as outlined above.

Figure 1. Conceptual approach to oversight of research that raises significant biosafety and biosecurity concerns as described in this report. This process includes federal, institutional, and investigator responsibilities at different stages throughout the research lifecycle.



7. Appendix A. Key current stakeholder responsibilities for the oversight of DURC and enhanced PPP research

	Overview of Key Responsibilities	
Entity	**DURC Oversight Framework**	**P3CO Framework***
Principal Investigator	• Continuously assess research to identify research that is subject to the policy and, if so, refer for institutional review • Ensure that laboratory personnel conducting research with any of the 15 agents/toxins receive education and training • Conduct DURC in accordance with the risk mitigation plan • Communicate DURC in a responsible manner throughout the research process, including at publication	• No requirements explicitly articulated; investigators and institutions contribute to federal reviews via the development and provision of material, as requested
Research Institution	• Establish and implement policies and practices for identification and oversight of DURC including a review entity and institutional contact for dual use research • Provide education and training and ensure appropriate review of research with DURC potential • Notify relevant federal agency/office of institutional review outcomes and of instances of non-compliance • Work with the funding agency to develop a risk mitigation plan, and ensure implementation of and adherence to approved risk mitigation plans for DURC	• No requirements explicitly articulated; investigators and institutions contribute to federal reviews via the development and provision of material, as requested
Federal Funding Agency	• Review research portfolios to identify DURC • Require supported institutions to implement DURC oversight and address reports of non-compliance • Work with investigators and institutions to develop a risk mitigation plan	• Conduct standard scientific merit review and refer proposed research being considered for funding that is reasonably anticipated to create, transfer, or use enhanced PPPs for departmental-level review • Provide relevant information and participate in departmental-level review, as requested

		• Consider the recommendations of the departmental-level review and make a funding decision • Report relevant information on funding decisions to the department and OSTP • If funded, ensure implementation of and adherence to terms and conditions of award including any additional risk mitigation measures
Federal Department	• Develop training tools and provide education and guidance to funding agencies, institutions, and investigators • Report aggregate information to the USG biannually • Periodically assess the impact of and update DURC policies as appropriate	• Convene a multidisciplinary group to review research referred by the funding agency • Critically evaluate the proposed research, including the risk/benefit assessment and proposed risk mitigation plan • Consider the eight criteria for guiding funding decisions and additional relevant information • Develop recommendations on acceptability for funding, including suggestions for additional risk mitigation measures and/or terms and conditions of award, if funded
U.S. Government (multiple Departments or Inter-Departmental common approach)	• Develop training tools and provide education and guidance to funding agencies, institutions, and investigators • Periodically assess the impact of and update DURC policies as appropriate	• Coordinate assessment of the impact on research programs and institutions, enhanced PPP research, and how to provide transparency, public engagement, and continued dialogue • Engage with other countries regarding oversight of enhanced PPP research and encourage development of harmonized policy guidance • Consider whether policy approaches should be proposed to enable oversight of relevant research activities regardless of the funding source