MITRE's Response to the OSTP RFI on Potential Changes to the Policies for Oversight of DURC and P3CO

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About MITRE

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MITRE has broad expertise in the life sciences, including biotechnology, immunology, infectious disease, microbiology, epidemiology, biology, and biomedical engineering, which it uses to provide subject matter expertise and technical awareness of biosafety and biosecurity analysis and assessment to numerous federal agency sponsors. This includes research oversight, facility evaluation, global health security, U.S. competitiveness in the biomanufacturing industrial base, policy analysis, and research program support with the goal of improving health outcomes and protecting the nation from infectious disease threats.

Introduction and Overarching Recommendations

MITRE is supportive of attempts to harmonize existing Dual Use Research of Concern (DURC) and Enhanced Potential Pandemic Pathogen (ePPP) oversight into a unified policy. Biological research involving pathogens can be risky but also highly beneficial. While there are concerns that creating stricter guidance will impede life sciences research, the biosecurity and biosafety risks of weak life sciences policies are too great to ignore.

It must be remembered that the intent of this unified policy is not to halt or impede research, but rather to ensure proper care, oversight, and protection are in place to prevent any unintended consequences or harmful outcomes from occurring. Alternative, safer methods for answering research questions should be considered and risk mitigation measures should be put in place where appropriate. While implementation of this policy could slow research to some extent, well-designed policy that is clear and easy to implement should not result in major delays.

It is crucial to strike a balance between ensuring responsible and safe conduct in life science research and fostering innovation that allows the U.S. to remain competitive in the international research, development and bioindustrial base landscape. As we harmonize these policies, it is imperative to develop an adaptable approach that supports scientific advancement, encourages international collaboration, and promotes the responsible sharing of knowledge and technology,

without introducing strategic vulnerability. By doing so, we can reinforce the U.S.'s position as a global leader in life sciences research without compromising safety, security, and public trust.

Questions Posed in the RFI

1. (a) What are the anticipated benefits and challenges of applying a Revised Policy, inclusive of both DURC and ePPP research, to the scope of entities outlined?

Overall, having a harmonized policy for oversight of different life sciences research that has consistent definitions, scope, roles, and responsibilities would help ensure that policies are being applied consistently. The current biosafety and biosecurity oversight policies are difficult to implement due to the overlap in terminology and scope that can lead to inconsistent interpretation by researchers and oversight groups. An appropriately designed Revised Policy would ensure that there is a single policy that users could review to ensure they are following best practices for life sciences research. However, implementation of a crosscutting policy that encompasses life sciences research in the United States and abroad would encounter challenges in enforcement.

The current DURC policy facilitates implementation by having clear criteria of what agents are covered and the types of experiments are of concern that are covered by the policy. On the other hand, the Potential Pandemic Pathogen Care and Oversight (P3CO) policy scope is broad and subjective. The harmonization of these opposing approaches will need to be done carefully to avoid introducing uncertainty, making implementation more challenging, and leading to uneven enforcement across the research community.

Additionally, the Revised Policy expands the scope beyond the previous DURC and P3CO policies. It will be difficult to educate the research community about the expansion of the policy's scope, bring in an increased number of experts to provide oversight for this research, and respond to an increase in workload. Both careful revision of policy text, and outreach and education for these new entities will be needed.

(b) What are the anticipated benefits and challenges of investigators and institutions having primary responsibility for identification of both DURC and ePPP research?

A risk to this approach is that there are widely different levels of expertise at different institutions. For example, some entities may have entire departments with significant expertise in pathogens, risk assessments, biosafety, and biosecurity. At other institutions this can be a single person with responsibility for providing oversight of all research. Because that one person cannot be an expert at all things it will take them longer to adequately research biosafety and biosecurity concerns for a much larger list of agents and toxins. Aggressively identifying and disseminating best practices might help address this. Development of training and frequently asked question (FAQ) lists, and staffing a reach-back center would also aid rollout of this policy.

Because much of the suggested revised language moves away from defined agent lists and a "checklist" approach, policy enforcements will be much more subjective. This can lead to dramatically different interpretations of risk and uneven enforcement. Unclear or subjective criteria will result in uneven initial screening, which could result in either potentially risky

projects not being caught or every project being sent back to the funding agency for further evaluation. This could cause delays in review and potential delays in performing important research.

A well-crafted policy can help prevent this. One approach is to train institutions to take a risk-based approach where, if there is any doubt or question, they flag the proposal and request the investigator consult directly with the funding sponsor for a final decision. This triage method would allow institutions to rapidly table proposals until a funding agency could conduct a risk benefit analysis of the proposed research approach. If the project was determined to be DURC or P3CO but still necessary, the Institutional Biosafety Committees (IBCs) would only then work with researchers to develop plans to ensure all safety and security concerns are addressed.

(c) What types of resources or tools would be useful for researchers and institutions to determine if their research falls into a revised policy scope that is risk-based rather than list-based, and adequately conduct risk assessments to identify DURC and ePPP research?

To ensure the success of the Revised Policy, it is crucial that additional funding is allocated to researchers and institutions for performance. Institutions are currently not funded to perform this type of activity. As such, the institutional overhead rate charged to recoup costs associated with this increased responsibility should be expected to go up. Additionally, best practices recommend that oversight committees include volunteers who are not associated with the research institution. Expansions of Revised Policy scope and institutional responsibility will increase the workload significantly. It may become more difficult to find volunteers willing to take on this additional workload. It should be expected that expansion in scope will lead to delays in research execution as researchers and institutions work through a much larger volume of research plans.

To facilitate the implementation of the Revised Policy, tools informed by decision science and risk assessments, such as decision trees, checklists, and FAQs, will help with implementation. These tools will help researchers and institutions navigate the complexities of the policy and make informed decisions based on their specific needs and circumstances. Additionally, a reach-back “help desk” should be established to provide further support and guidance to researchers and institutions. This service will ensure that all questions and concerns are addressed promptly and effectively.

Moreover, an educational and awareness campaign should be launched alongside a series of webinars to inform researchers and institutions about the Revised Policy and its implications. This campaign will help foster a deeper understanding of the policy and its benefits, while also addressing any potential misconceptions or concerns. By actively engaging with the research community, the campaign will aim to promote transparency and collaboration.

Lastly, aggressively identifying and disseminating best practices should be a key priority. By actively seeking out and sharing proven strategies and techniques, researchers and institutions can learn from one another and continually improve their performance. This collaborative approach will not only drive progress within individual institutions but also contribute to the overall advancement of the research community.

2. a. Considering the diversity of federally-funded research settings and portfolios, how would adoption of NSABB's Recommendation 10.1 affect policy implementation and research programs at the institutional level?

The implementation of the Revised Policy would have significant implications at the institutional level, particularly with regard to the increased number of proposals requiring review by the IBCs. This surge in proposals would not only place a greater demand on IBC resources but also necessitate a more efficient and streamlined review process to ensure timely and effective evaluations.

Additionally, the Revised Policy would lead to an expansion of the type of expertise required on institutional review committees. This means that committees would need to diversify their membership to include experts from various fields, ensuring comprehensive evaluations of proposals. This broadening of expertise would help identify potential risks and benefits associated with the research and contribute to a more informed decision-making process.

Moreover, the Revised Policy would significantly expand the range of entities it applies to, extending from several hundred to any entity working with a pathogen, toxin, or agent. Some of these entities may not have regular interaction with authorities and oversight, which poses challenges in terms of monitoring and enforcement. Identifying and maintaining an up-to-date list of these entities would likely be a considerable undertaking, as there is currently no mechanism in place to capture this information.[1]

b. Would a modification of Recommendation 10.1, in line with the outlined scope of pathogens above, be useful for policy implementation? What specific benefits, challenges, and/or gaps are anticipated by this revised scope?

The proposed option to expand the list of DURC from the current 15 agents to 68 Federal Select Agents and Toxins, as well as including work performed in high containment laboratories or within high-risk groups, offers several advantages. One of the key benefits of this expansion is the creation of a well-defined list with clearly established screening criteria, which would facilitate the process of identifying relevant research projects and ensuring compliance with the policy.

Furthermore, the agents in the expanded scope have already been carefully vetted to identify agents that have the "potential to pose a severe threat to both human and animal health, to plant health, or to animal and plant products." A major advantage of this language is the harmonization of recommendations that currently exist and are well understood by the life sciences research community.

Most IBCs are already familiar with screening protocols involving these agents and have established review committees for high containment laboratories. This existing knowledge would

[1] R. Myers. Report on the Health and Safety Issues Associated with High Containment Laboratories in the State of Maryland. 2013. Workgroup for Biocontainment Laboratories Oversight, https://msa.maryland.gov/megafile/msa/speccol/sc5300/sc5339/000113/018000/018731/unrestricted/20132793e.pdf.

make the implementation of the expanded list a relatively straightforward process that does not overburden investigators and institutions.

The increased screening under this option would effectively capture most high-risk research, ensuring that appropriate oversight and safety measures are in place. Additionally, the policy's application to high containment laboratories would also cover unknown pathogens, further enhancing the scope and effectiveness of the Revised Policy.

c. Are there other risk-based approaches that would expand the scope beyond the current list of 15 agents and toxins provided in the DURC policy that would facilitate the identification of research that poses significant risks by investigators and institutions while not resulting in undue burdens?

MITRE considered several other options, including:

- Just expanding to include the BSAT (68) agents and not including the other two criteria
- Expanding from the 15 DURC pathogens to the NIAID Category A, B, or C priority pathogens
- Using the Especially Dangerous Pathogens list from the DTRA BTRP program
- International best practices

Each list is slightly different and has advantages and limitations. The proposed language in option 2.b includes all the agents on these lists and has the advantage of being broader and more widely known.

d. Given the possible revised scope of research requiring review for potential DURC, what modifications, if any, to the current DURC policy list of 7 experimental effects should be considered for a Revised Policy that captures appropriate research without hampering research progress?

MITRE believes the current 7 experiments remain valid and provide a strong conceptual foundation for the Revised Policy. The 7 experiments as written also cover the proposed expanded list of agents for consideration, which would also cover agents and toxins that are not just human pathogens. Therefore, MITRE does not believe revisions are needed.

e. What resources or tools would be valuable to assist with implementation of a DURC policy with a scope that is revised to include more than the current list of 15 agents and toxins?

In order to effectively expand the implementation of the Revised Policy, several tools and resources must be employed, many of which have been discussed in previous answers. The use of tools such as decision trees, checklists, and FAQs, informed by decision science and risk assessments, will greatly assist researchers and institutions in understanding and implementing

the Revised Policy. These tools will streamline the process of navigating the policy's complexities and ensure informed decision making in line with the policy's requirements.

An education and awareness campaign, coupled with webinars, would be instrumental in familiarizing researchers and institutions with the policy changes. In addition to these tools, investigating innovative technologies that could enhance the implementation of the policy should be considered. This could involve exploring new methods of data collection and analysis, or the development of novel risk assessment tools, to further support institutions in complying with the policy.

Lastly, creating an easy-to-understand website with accessible forms and resources for researchers and institutions will be crucial in facilitating the implementation process. By providing a centralized platform for information and guidance, researchers and institutions can quickly access the resources they need to navigate the Revised Policy effectively.

3.a. How would the change in the definition of PPP affect the overall scope of a Revised Policy and its subsequent implementation?

The current definition of the Revised Policy scope creates more confusion due to the usage of terms like "or," "and/or," the inclusion of "likely moderately," and "highly." It would be beneficial to use simplified language to make the policy easier to understand. One of the challenges is that the definition of revised PPP remains subjective, and there needs to be a clear distinction between what is considered "moderate" versus "likely." Without explicit criteria and definitions, the burden falls on researchers and institutions to interpret the policy. Additionally, it remains unclear who will determine whether a given pathogen is likely to have specific impacts and how this will be decided.

On examining the policy, it appears that pathogens must meet either of the first two clauses and have at least one feature of the third clause. Including an agent's likely impacts on important societal systems is a sensible approach. By testing some examples with this new language modification, it becomes apparent that the policy would include and exclude several use cases. For instance, the new policy would cover anthrax, which has a high mortality rate but not a high transmission rate. On the other hand, it would exclude something like a cold virus, which is highly transmissible but not a severe public health threat. After running multiple examples, it seems that this version of the policy works better than the previous one.

However, some questions remain, such as whether HIV or Creutzfeldt-Jakob disease would be included in the policy's scope. To address this, the committee should consider expanding the clause "the capacity of public health systems to function" to include healthcare systems, as it is currently unclear if these would be considered under the policy.

b. One possible modification to the NSABB PPP definition is to specify a respiratory route of transmission within clause (1). Would that definition of PPP be an appropriate scope to mitigate risks and enhance effective implementation?

We do not think the policy should be limited to the respiratory route of transmission. The respiratory route is the most important from a pandemic potential perspective. However, diseases such as cholera, Ebola, Hepatitis B, and HIV also present clear threats to public health and national security, and these pathogens have exhibited pandemic spread in the past. Other potential routes of PPP transmission shouldn't be excluded.

c. Do you have additional suggestions to modify the PPP definition to mitigate the most significant risks not currently addressed and enhance effective implementation, while limiting negative or unintended consequences and burden on researchers, institutions, and the Federal government?

One way to make the policy easier to implement would be to rewrite it in a checklist form, similar to the approach used in DURC. This could make it clearer for users to understand the policy's requirements. Additionally, incorporating a decision tree into the definition could help clarify what is included within the scope of the policy. As it stands, the definition can be confusing due to the use of "and/or" between clauses (1) and (2), while the last clause (3) is required for the policy. To avoid confusion, it would be beneficial to revise the language and structure of the policy to make it more comprehensible.

Providing clear definitions for terms like "moderate," "highly," "likely," "significant," and "severe," along with relevant examples, could greatly aid in the policy's implementation. This would ensure that users have a better understanding of the criteria and can apply the policy more effectively. Lastly, it is important to identify the mechanism or protocol for handling situations where an experiment meets the definition of PPP. Establishing a clear process for addressing these cases will not only streamline the implementation of the policy but also ensure that it is applied consistently and effectively across various scenarios.

d. Are there characteristics related to human pathology, pathogen characteristics, or other features that would be helpful to clarify the intent of "moderately virulent"? Are there characteristics related to human pathology that would be helpful to clarify the intent of "moderately transmissible"?

Moderately virulent diseases can be characterized by their impact on morbidity, which includes not only the direct effects on an individual's health, but also the broader societal consequences such as work absence, hospitalization, and school closures. These repercussions can disrupt daily life and place a strain on healthcare systems, further emphasizing the importance of understanding and mitigating the spread of moderately virulent diseases.

It is essential to recognize that certain subsets of the population are more at risk for diseases, such as elderly, young, and immunocompromised individuals. These groups may experience more severe symptoms or complications, and thus require additional attention and resources to ensure their protection from moderately virulent diseases. Additionally, long-term health consequences should be considered when evaluating the impact of a disease.

Metrics such as Quality-Adjusted Life Years and Disability-Adjusted Life Years can help quantify the lasting effects of diseases with long-term sequels, such as Long COVID-19. By understanding the potential long-term health implications of a disease, public health officials and medical professionals can make more informed decisions regarding treatment and prevention strategies.

Finally, in order to effectively assess the transmissibility of a disease, epidemiologists rely on the effective reproduction number (Rt). This measurement is critical in understanding how rapidly and widely a disease may spread within a community. Establishing agreed-on criteria for evaluating the Rt can help researchers and healthcare professionals better predict and manage the transmission of moderately virulent diseases, ultimately contributing to the overall health and well-being of society.

4.a Does this definition of "reasonably anticipated" provide additional clarity to ensure greater consistency in identifying research that falls within scope of the Revised Policy? What modifications to this definition (if any) would be most helpful?

While purposefully and thoughtfully defining key terms within guiding policy documents is needed, the proposed definition remains convoluted and confusing. It replaces the "reasonably anticipated" phrasing with another ill-defined term, "non-trivial." While the definition does clarify that scientific expertise is necessary for making judgments, it also highlights the need for risk assessment knowledge to apply this definition across various institutions. Nevertheless, there is a risk that this updated definition may be applied inconsistently across institutions without further clarification. As much clarity, specificity, and consistency as possible is desired.

Overall, these definitions should be clear and concise with clearly defined terms, concepts, and responsibilities. Replacing ambiguous or open-ended statements with specific examples, numbers, or scenarios in addition to incorporating quantifiable terms will help in assessing and identifying research that falls within the Revised Policy.

5. a. Should exemptions for certain activities be included in a Revised Policy?

No, a Revised Policy should not include blanket exemptions for certain activities. Instead, a proposed waiver process could provide much of the flexibility afforded by the exemptions while increasing transparency and further minimizing risk.

b. What are the benefits and drawbacks of including exemptions for domestic and international pandemic preparedness, biosafety, biosecurity, and global health security?

While exemptions may enable the conduct of certain activities related to preparedness and response, those activities do present relevant risks that should be accounted for. It should be noted that the goal of the Revised Policy, as was the case with the legacy policy, is to minimize risk associated with certain research and development activities, not to prohibit those activities.

c. If exemptions are included, how could they be bounded to maximize safety and security and minimize negative impact on domestic and global public health including outbreak and pandemic preparedness and response?

Instead of blanket exceptions, the Revised Policy could introduce a waiver process so that there is a mechanism to enable work that is clearly in the interest of public health and global health security but that also provides an opportunity for additional scrutiny and deliberation if warranted. Such a process could and should be structured such that it is minimally burdensome on investigators and local reviewers, in part by including a reasonable deadline for review as well as, potentially, an appeals process.

The implementation of a waiver process for certain research activities would have the additional, spillover benefit of increasing the transparency of the research enterprise as a whole. If such a process was to be put in place, it would be possible for federal officials, academics, and others to better quantify how often a given experimental approach is occurring and to track trends over time. By contrast, under a regime that includes exemptions for surveillance and vaccine development activities, those opportunities for data collection and analysis are lost.

The proposed waiver process could act as a middle ground between full review and a blanket exception to capture important information about certain activities while minimizing the burden on institutions that perform experiments (i.e., certain kinds of vaccine research and development) that may qualify under the policy.

6.a. Is there a subset of such *in silico* research that should require risk assessment and review in a Revised Policy, and if so, how should this research be defined so that the Policy captures the appropriate research without hampering activities with limited biosecurity risks?

There are various concerns regarding biological research carried out using *in silico* approaches. These include the utilization of Artificial Intelligence (AI) platforms for nefarious purposes such as the circumvention of current DNA synthesis screening methods, the modification of existing pathogens, or the *de novo* creation of novel biological threats. Despite these concerns, and the clear need for policies intended to anticipate and prevent them, the Revised Policy is focused on research that employs *in vitro* and *in vivo* methodologies. In order to expand the scope of the policy to include *in silico* research, it would be necessary to collaborate with different stakeholders and institutions, including private sector developers of AI platforms. These groups would play a critical role in assessing the risks and potential benefits associated with *in silico* methods, as well as providing input on how to regulate and monitor these techniques effectively. The implementation of an expanded policy that includes *in silico* research would likely differ significantly from the current or Revised Policy, which mostly applies to life sciences researchers and administrators in academic institutions.

Moreover, it should be noted that trusted and federally funded institutions could use *in silico* research as a safer alternative to conducting experiments covered by the Revised Policy. Arguably, *in silico* methods, which involve computer simulations and modeling, can offer a less risky way to study biological systems compared to traditional wet lab techniques. This could

help minimize the potential for accidental release or misuse of harmful biological agents. Importantly though, once certain *in silico* studies transition into a wet lab setting (i.e., involving *in vitro* or *in vivo* methodologies), they would fall under the jurisdiction of the Revised Policy.[2]

b. If a new category of research, similar to the examples provided above, were to require risk assessment and review in a Revised Policy, what would be the benefits and challenges with implementation?

The AI regulatory landscape is evolving rapidly. For example, the National Institute of Standards and Technology has developed an AI Risk Management Framework, which aims to provide a structured approach to assessing and mitigating risks associated with AI technologies. Similarly, multiple pieces of legislation have been introduced that have the goal of strengthening the governance of emerging AI platforms, including one that would create a new federal agency. By and large, however, most of these frameworks are not specifically designed to address the unique challenges and concerns related to the confluence of biological research and AI. As a result, there is an urgent need to assess and address this evolving class of technological risk and to develop a baseline understanding of what constitutes "risky" in the *in silico* space and who the most important actors are. Expanding the Revised Policy to include the risk assessment and review of a limited number of *in silico* studies would accomplish this goal, but implementation is likely to be challenging.

As noted above, the covered entities would necessarily include private sector technology developers as well as academic researchers. There would need to be significant outreach to actors that likely have a different understanding of risk and that operate under different incentive structures. It is also unclear whether these private sector stakeholders would be covered under the Revised Policy, as many are not funded by the federal government to conduct research or product development. Finally, it is not clear who would be responsible for assessing risks and reviewing the *in silico* research captured under an expanded policy, as there is not an analog to the institutional review board in the private sector. It should also be noted that, while the adoption of *in silico* methodologies could reduce the need to conduct potentially risky experiments and thereby reduce risk overall, expanding the Revised Policy to capture *in silico* research in a way that is overly broad could also hinder the ability to answer critical questions, such as understanding how COVID-19 strains could evolve to evade therapeutics and vaccines.

While a limited number of *in silico* studies may require risk assessment and oversight in order to protect public health and safety, these issues are sufficiently complex to warrant their own policy process that can more fully address the associated risks and trade-offs.

[2] Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA. 2010. Department of Health and Human Services, https://www.phe.gov/Preparedness/legal/guidance/syndna/Documents/syndna-guidance.pdf.