Response to OSTP RFI on Policies for Oversight of DURC and P3CO Framework

Submitted by the following in their individual capacities:

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Thank you for the opportunity to provide comments on the Request for Information: Potential Changes to the Policies for Oversight of Dual Use Research of Concern (DURC) and the Potential Pandemic Pathogen Care and Oversight (P3CO) Policy Framework. Responses below respond to the specific questions indicated in the RFI.

The questions in this RFI understandably seek feedback on the potential implications and burdens of a Revised Policy on scientists and institutions engaged in covered research activities. However, such framing on its own may inadvertently undervalue the arguably greater importance of protecting the well-being of humans, animals, plants, and the environment from especially dangerous DURC and enhanced potential pandemic pathogen (ePPP) research. Reducing the risks of accidental or deliberate creation of novel organisms with epidemic or pandemic potential and their release, while not unnecessarily impeding science, is the central goal. Research activities must be seen in the broader and more significant context of the USG's responsibility to reduce risks of accidental or deliberate pandemics to which a narrow and limited segment of research—ePPP research—may contribute if un- or underregulated.

The general population of the United States has a fundamental interest in such protection. All Americans have the potential to be harmed if ePPP research increases pandemic risk, and they have neither consented to nor in most cases been informed of the risk, despite public dollars often funding this research. Given the potential for a dangerous pathogen to cross national borders, the global population also has a legitimate interest in such protections. It is important to keep this balance in mind with all comments below and give due weight to public safety concerns relative to the concerns of researchers and research institutions.

1. **The NSABB recommended that USG develop an integrated approach to oversight of research that raises significant biosafety and biosecurity concerns, including ePPP research and DURC (Recommendation 1). By merging the existing Federal DURC, Institutional DURC, and P3CO policies into a harmonized policy, a merged policy could potentially adopt the institutional applicability outlined in the Institutional DURC policy framework, making the following entities subject to a Revised Policy:**
    - **U.S. Government departments and agencies that fund, sponsor, or conduct life sciences research.**
    - **Institutions within the United States or its territories that both:**
        - **Receive U.S. Government funds to conduct or sponsor life sciences research; and,**
        - **Conduct or sponsor research that is within the revised scope, regardless of the source of the funding for the specific project.**
    - **Institutions outside of the United States that receive U.S. Government funds to conduct or sponsor research that falls under the scope.**

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 above?

An inclusive, integrated policy is desirable and makes sense. It minimizes the possibility of redundancy (overlap) and contradictory language or meaning that could arise from separate policies. It encourages harmonization, streamlining, and clarity, and it reduces the number of separate policies about which stakeholders must be educated.

The benefits of applying a Revised Policy to all institutions that conduct research covered in the scope of this policy, whether or not the research is funded by the USG, is that it will provide governance intended to protect the public from the very serious consequences of accidental or deliberate events that could result in an epidemic or pandemic, originating from any institution conducting such research. From the point of view of the US public (or other countries' populations), the funding source for this type of research also does not matter; the risks would be the same, independent of funding source. A policy that covers a range of entities, not only those receiving USG funding, will also be easier for US diplomats to explain and defend. There is clear precedent for such forms of research oversight, including research involving human subjects and other vertebrate animals.

To apply the Revised Policy to US-based institutions that are not funded by the USG will require determining the best legal approach for doing so and engaging in rulemaking. One prior analogue worth considering is Human Subjects Research. Human Subjects Research rules apply to "***all*** [emphasis added] research involving human subjects conducted, supported, or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research. … It also includes research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States."[1] This rule clearly applies to both public and private entities, so long as a federal department or agency takes appropriate administrative action to apply the policy. Unlike Human Subjects Research rules, however, the Revised Policy being considered in this RFI is focused around a much smaller subset of research and therefore would be less complex and more circumscribed in scope.[2]

Another approach would be to follow the model set out in the NIH guidance on recombinant DNA research, to which even institutions not funded by NIH are encouraged to comply.[3] Even privately funded projects employing recombinant DNA must adhere to the NIH Guidelines if they are being carried out at, or funded by, an organization that has any NIH contracts, grants, or other support for this type of research.[4] This is a feasible way of expanding the Revised Policy to private entities absent rulemaking as outlined above. However, due to the importance and magnitude of the potential harm of DURC and ePPP research compared to recombinant DNA research, a regulatory approach as outlined above would be more appropriate than a voluntary guidance approach.

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[1] 45 CFR §46.101(a)

[2] For example, language included throughout 45 CFR §46.101, not only subsection (a).

[3] See Section IV-D. Voluntary Compliance on page 35 of *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) April 2019*

[4] See *Reminder of NIH Policy for Enhancing the Science, Safety, and Ethics of Recombinant DNA Research*

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

One benefit of investigators and institutions taking primary responsibility for identifying DURC and ePPP research is they have the earliest and clearest insight into whether the work falls within scope. When it does fall within scope, investigators and institutions would be best positioned to find alternative lower-risk paths for pursuing their work. If they cannot identify lower-risk approaches, they could conduct an assessment to weigh the potential benefits and risks of conducting the proposed research. This approach also reduces the likelihood that important DURC or ePPP risks are missed by federal funders—or other funders—who may not have full access to the details and background of the proposed experiments. An additional possible benefit of this approach is increased awareness of DURC and ePPP issues among investigators, similar to how reducing the number of vertebrate animals used in experiments and reducing the discomfort they experience is now an ingrained principle among life sciences researchers. Giving investigators and institutions primary responsibility for identifying DURC and ePPP research will require education and training. The issuance of guidance on this by the federal government for researchers, research institutions, and other affected entities, as is standard practice alongside the publication of new policies, programs, and regulations, would address this challenge.

While researchers and institutions are best placed to identify ePPP and DURC risks early in the proposal process, the federal government also will need to independently assess the value and risks of proposed research in accordance with the Revised Policy. For USG-funded research, the government could direct members of a Study Section or other body charged with scientific review to flag concerns about DURC or ePPP issues, similar to the way Study Section members are asked to flag issues of human subjects, animal welfare, and data availability in current NIH reviews. The flag could trigger administrative consideration by the funding agency with an obligation to provide a written justification for why the study is or is not being referred to department-level review.

Reviewing proposals at the time of funding, while critical, is necessary but not sufficient given that scientific plans outlined in proposals change over the course of a research project, usually for many good and legitimate reasons.[5,6] Procedures for flagging ePPP and DURC concerns need to be in place at least for annual progress reports; ideally there would be a mechanism whereby investigators could flag potential concerns at any time in the grant cycle. The proposal below to have a contracted Institutional Biosafety Committee (IBC)-like mechanism could be expanded to provide this service.

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?

Following issuance of the Revised Policy, the federal government should issue clear guidance (including FAQs and illustrative examples) that further help to describe the types of research that fall within and outside the purview of the Revised Policy. Examples of actual or scenario-

[5] https://doi.org/10.1126/science.1142873

[6] https://doi.org/10.1126/science.adf6020

based research projects and an analysis of those that would and would not fall within the requirements of the Revised Policy will be helpful. Also of high value will be to convey past examples of work that were reviewed and raised concerns and, where appropriate and relevant, how concerns were addressed. These types of case studies could be anonymized to keep the specific institutions and researchers from being named. The current practice is to release almost no information about these proposals—the problem with this approach is that it is very difficult for federal government officials engaged in review of this work, researchers, or institutions to receive feedback and learn over time.

Providing guidance for newly released policy frameworks is standard practice and extremely helpful in educating affected entities and providing uniform interpretations of terms that will assist in broad compliance with the policy.[7] For instance, when HHS issued the HIPAA Privacy Rule and covered entities were concerned about appropriate implementation, HHS then issued extensive guidance and tools to assist HIPAA-covered entities in implementing the Rule. Among other things, guidance was provided to help covered entities identify and document "reasonably anticipated" threats to electronically protected health information subject to HIPAA oversight.[8]

If the Revised Policy is implemented via rulemaking, the guidance should similarly provide more detailed instructions and criteria for how researchers and institutions can perform risk assessments and how best to identify relevant potential benefits and risks related to the work. To assist institutions with interpretation and implementation, a centralized IBC that is virtual or contractual in nature could provide institutions with the ability to implement a Revised Policy. Another approach is to require investigators and institutions to identify, review, assess, and mitigate the risks of covered ePPP and DURC research. They would have all the information needed to make informed decisions. However, PIs, biosafety officers, institutions, and others within the research ecosystem have varying degrees of knowledge and experience with DURC/ePPP. A significant education, training, and communication campaign will be needed to help the life sciences research community come into compliance.

Another challenge to implementing NSABB Recommendation 10.1 will be in communicating this change to the research community; this will require a dedicated communication effort to reach researchers and institutions. It will be necessary to designate sufficient resources so that the federal government can identify when further review is needed without conflicts of interest, and, when it is needed, provide the independent review of research that falls within the Revised Policy scope. The reviews for ePPP work in the last few years have been reported to be quite slow, as have responses to informal inquiries about research that did not turn out to require review. For proposals not to languish and be badly delayed, more human and financial resources would need to be dedicated to this work.

Even the best-informed formulation of the Revised Policy will need to evolve as experience is gained with its application and as the landscape of risks and benefits changes. We strongly urge the incorporation of a specific requirement to review and make recommendations for updating guidance no less frequently than every 2 years. Within the Revised Policy rulemaking, it would be useful to include language that anticipates the future issuance of guidance and the

[7] For example, see guidance contained in the HHS Guidance Portal

[8] 45 CFR §164.306(a)(s) and §164.316(b)(1)(ii) on how to identify this work and understand the scope of the policy

ability to refine terms over time as more experience is gained, in addition to the comprehensive review on a schedule suggested above. As an example, the HHS Policy for Protection of Human Research Subjects stipulates: "Federal departments or agencies implementing this policy shall: (i) Upon consultation with appropriate experts (including experts in data matching and re-identification), reexamine the meaning of 'identifiable private information,' … and 'identifiable biospecimen,' … This reexamination shall take place within 1 year and regularly thereafter (at least every 4 years). This process will be conducted by collaboration among the Federal departments and agencies implementing this policy. If appropriate and permitted by law, such Federal departments and agencies ***may alter the interpretation of these terms, including through the use of guidance*** [emphasis added]."[9] Such language would provide flexibility and ensure that certain Revised Policy definitions are reevaluated regularly, keeping pace with technological advances and the dynamic threat landscape.

2. Currently, the scope of the DURC policies is research that uses one or more of 15 listed agents or toxins and that produces, or is anticipated to produce, any of seven listed experimental effects. The NSABB recommended that the scope of research requiring review for potential DURC should 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 outlined in the DURC policy (Recommendation 10.1).

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?

It is widely recognized that relying on the 15-agent list-based approach to risk assessment is outdated and fails to address ever-growing vulnerabilities as scientific technology advances. We are therefore supportive of NSABB's Recommendation 10.1, which rightfully moves beyond the list-based approach. Adopting Recommendation 10.1 would result in an increased number of projects and proposals requiring oversight, relative to the number that currently qualifies, with attendant increased costs. We view this result as a necessary and important consequence in moving toward a more effective and holistic oversight regime. Opponents of broader oversight argue that more oversight and governance will chill scientific investigation and reduce scientific freedom. However, it is the case that (i) the scope of experiments covered by the Revised Policy is still extremely small compared to the overall scientific enterprise and even compared to virology and microbiology as a whole; (ii) we commonly and correctly accept restrictions for far less consequential reasons than reducing pandemic risk, such as preventing social stigma for subjects in a small research study or reducing animal suffering in research; and (iii) failing to oversee such work adequately could potentially lead to future accidents or deliberate events that trigger unreasonable or knee-jerk restrictions on science. It will be important to provide guidance and support to scientific institutions as they gain experience over time in reviewing DURC 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."

While moving from a list-based approach to DURC to an approach that focuses on potential outcomes of DURC is likely to expand the number of proposals that receive initial consideration

[9] 45 CFR §46.102

for being within scope of the Revised Policy, the vast majority of experiments—including those with major pathogens such as influenza, coronaviruses, HIV, tuberculosis, and others—will clearly fall outside the requirements for enhanced review, and it will be crucial to have in place sufficient resources to ensure that such experiments are rapidly classified as not requiring enhanced review.

b. Rather than including any pathogen within the scope of DURC review, one possible modification of Recommendation 10.1 would be to include DURC experiments that utilize:

i. HHS and Overlap Biological Select Agent and Toxins (BSAT) List and/or

ii. Pathogen risk group (RG) classification of 3 or 4 and/or

iii. Any pathogen where the conduct of work (e.g., one of the DURC experimental categories) would require biosafety level 3 or 4 containment.

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?

We oppose limiting the scope of DURC review to the BSAT list and/or the pathogen risk group (RG) classification of 3 or 4 and/or any pathogen requiring biosafety level 3 or 4 containment. The 2 basic problems with such a set of modifications are that (1) the focus of the Revised Policy would be on the starting organism or biological entity rather than on the anticipated products of the proposed work; and (2) the Revised Policy would depend upon uniform recognition of an organism or biological entity based on its name—and taxonomic designations are imprecise and misleading, especially in a world of increasingly powerful biological engineering approaches.[10] If research is proposed that could create more transmissible organisms with the potential to lead to epidemics, or more virulent or lethal outcomes of already epidemic- or pandemic-capable organisms or strains of organisms, we recommend this work be covered. Thus, we recommend implementing Recommendation 10.1 in its unmodified form, regardless of whether an organism was on the list of 15 or other list, because that is what is in the public interest.

An important benefit of implementing Recommendation 10.1 unmodified is that it would sensitize researchers and institutions that are not now aware of these risks or public concerns, perhaps working on organisms that could be made more transmissible or more lethal. Covering this research by the Revised Policy would raise awareness and direct them to consider benefits and risks during the research proposal stage.

When considering biosafety and biosecurity risks, the USG should place the highest concern on those experiments that could result—in the event of an accident or deliberate misuse—in (1) uncontained community spread of a novel pathogen or variant strain of a pathogen within the human, animal, or plant communities or the environment, or (2) uncontained community spread of a novel pathogen that was already transmissible and capable of epidemic or pandemic spread but now is more harmful. An independent federal review of risks and potential benefits of this kind of work should occur, regardless of whether the agent is on the current BSAT list, has an RG classification of 3 or 4, or is required to be handled in BSL 3 or 4 facilities. The risks to the public do not depend on the nature of the starting organism at the beginning of the proposed

[10] https://doi.org/10.1038/nrmicro2299

work, nor on what we call the organism—if we are even able to give it a name—but rather on the nature of the organism or product that is expected to result from the proposed work.

We recognize the challenge of drawing clear lines in the absence of a list. We suggest that lists could be incorporated into the Revised Policy in an illustrative capacity to increase understanding of the Revised Policy, while maintaining that, regardless of whether a pathogen started on a list, if the research could lead to increased transmissibility of a pathogen, or increased virulence in a transmissible organism, it would be covered by 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?

We support the adoption of NSABB Recommendation 10.1. It is more meaningful from a risk avoidance perspective to rely on the phenotypic properties of organisms created during research activities rather than their starting taxonomy. The phenotypic properties most relevant to increasing risk of pathogens are transmissibility and pathogenicity. If researchers propose or can anticipate that the result of their work could be novel transmissible pathogens or strains of pathogens or result in already transmissible organisms that are more lethal or virulent, then the burden of including that work in the Revised Policy is not "undue." It does not make scientific or policy sense to limit the public concern around this work to a list of only 15 agents. The potential outcome of the work is the concern to the public, not what list the organism was on or name it had to start.

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?

To the extent that work within any of the 7 categories could reasonably anticipate creating novel pathogens or strains of pathogens that are capable of sustained community transmission, OR create more lethal or virulent pathogens or strains of pathogens that were already capable of community transmission, those experiments should continue to be covered. No modifications to the current list of 7 experimental effects are necessary.

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?

The NSABB has previously provided valuable guidance on many of these issues, and it could be called on again to guide the development of education and communication strategies and enhanced oversight infrastructure regarding a Revised Policy that has a scope beyond the original 15 agents and toxins. The federal government should issue guidance, tools, and scenarios for researchers and research institutions to assist them in determining whether their work falls within the definition and scope of DURC as set forth in the Revised Policy, and then ensure that the needed resources are made available.

3. **A PPP is currently defined in the P3CO policy framework as: "a pathogen that satisfies both of the following: 1. It is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations; and 2. It is likely highly virulent and likely to cause significant morbidity and/or mortality in humans." The NSABB recommended that the definition of PPP be modified to: (1) Likely moderately or highly transmissible and likely capable of wide and uncontrollable spread in human populations; and/or (2) Likely moderately or highly virulent and likely to cause significant morbidity and/or mortality in humans; and, in addition (3) Likely to pose a severe threat to public health, the capacity of public health systems to function, or national security" (Recommendation 2).**

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

The NSABB-recommended change in the definition of PPP would include pathogens that are likely moderately or highly transmissible and likely capable of wide and uncontrollable spread in humans; 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, public health systems, or national security. Adoption of this recommendation would necessarily include within scope work that was not previously covered, as the prior policy required both high virulence and high transmissibility be present. However, the framing of this new language and the inclusion of the final clause ensures that covered work would in fact entail significant risk. In practice, a "severe threat to public health" should be interpreted to mean the creation of novel transmissible organisms that can spread widely in the population, or the creation of pathogens that were already capable of spreading widely in the population but are now more virulent or lethal.

Effective implementation would require definitions of the terms "moderately transmissible" and "highly transmissible." We propose defining moderately transmissible as an organism potentially capable of community spread, potentially having a value of R_0>1 if it infected a member of the population in the community where the experiment is being performed. Any novel organism generated in the laboratory that is capable of community spread—"moderately transmissible"—should be covered by this Revised Policy. The term "highly transmissible" could be defined as the capacity for rapid and wide epidemic spread—such as viral diseases like SARS-CoV-2, influenza, measles, chickenpox, etc.—corresponding perhaps to an R_0>=2 in the population in which the work is being performed. Research that can result in that kind of spread also should clearly be covered by the Revised Policy. We note[6] that SARS-CoV-2 (COVID-19) in its earliest form was at least moderately transmissible (early estimates of R_0 in the range of 2-3) and moderately virulent (less than 1% infection-fatality rate in a large majority of the population) yet caused the most damaging pandemic in at least a century. Failing to modify the policy could mean that research anticipated to produce a pathogen with the properties of SARS-CoV-2 would be outside the scope of the policy. Any agent that is capable of uncontrollable spread, if released, would no longer be under the control of scientists, public health, or anyone else. This is a circumstance for which significant preventative efforts and clear governance through a Revised Policy are justified.

We recognize that it is difficult to predict the likely virulence or transmissibility, as defined using these population-level definitions, when the experiments performed are in cell culture

or animal models rather than human populations. However, some general principles could be adopted and illustrative scenarios used as part of the Revised Policy or as supplementary guidance to assist investigators, institutions, and agencies in assessing whether proposed work falls under the Revised Policy. For example, we suggest that:

- Studies using an agent that is already highly or moderately virulent or highly or moderately transmissible in humans and selecting for increases in one or both properties in an animal known to resemble humans in relevant respects (eg, ferrets for influenza transmissibility[11]) are presumptively subject to expanded review. Examples would include the 2012 publications about selecting for airborne ferret transmission in influenza H5N1.[12,13]

- Studies that involve recombination, reassortment, or similar processes in vitro or in vivo between genetic material from pathogens, either of which has moderate or high virulence or transmissibility, would presumptively fall under expanded review. Examples would include reassortment of avian H9N2 and human H3N2 influenza viruses[14] and potentially recombination between clades of poxviruses showing different levels of virulence and transmissibility in humans.

- Studies that involve deliberate pathogen adaptation to a small animal model, such as a mouse, that is not thought to be a good model for human-to-human transmission but is used for testing countermeasures such as drugs or vaccines, would presumptively NOT fall under the Revised Policy, if there were no deliberate selection pressure applied for airborne transmission. Examples would include adaptation of MERS virus to mice.[15]

We suggest that additional illustrative examples like these be provided to help investigators and evaluators navigate the conditions, emphasizing that to fall under the scope of the Revised Policy, work must satisfy either or both of the first 2 conditions (virulence and transmissibility), plus the third (severe threat to public health).

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?

It is not advisable to limit PPP to those that are respiratory transmissible. In practice, the most likely organisms to be covered by this Revised Policy as written are those that are capable of sustained respiratory transmission in the community. Other cases are worth consideration, however, such as research that could make cholera more virulent or more transmissible via the fecal-oral route. Work such as this should be reviewed under the Revised Policy because in low- and middle-income country settings, such strains could lead to more widespread or more lethal epidemics. Research that has the potential to result in novel organisms capable of sustained community transmission or result in transmissible organisms that are made more lethal or virulent should be covered by this Revised Policy.

[11] https://doi.org/10.7554/eLife.07969

[12] https://doi.org/10.1038/nature10831

[13] https://doi.org/10.1126/science.1213362

[14] https://doi.org/10.1371/journal.pone.0002923

[15] https://doi.org/10.1038/nmicrobiol.2016.226

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?**

We suggest that the focus of the Revised Policy be on research that could result in novel pathogens capable of sustained transmission in humans, animals, or plants, whether through the addition of this function to a pathogen that does not currently have it or through enhancement of that ability in a pathogen by making an already transmissible or virulent pathogen more so.

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"?**

We propose that "moderately virulent" be defined as capable of causing human, animal, or plant illness that results in impairment of at least some core function(s), and that "moderately transmissible" be defined as capable of sustained community transmission (R_0>1).

4. **A Government Accountability Office (GAO) report from January 202310 recommended that the Department of Health and Human Services funding agencies should develop and document a standard to define "reasonably anticipated" to ensure consistency in identifying research that falls within scope of a Revised Policy. One possible definition of "reasonably anticipated" is: "'Reasonably anticipated' describes an assessment of an outcome that an individual with scientific expertise relevant to the research in question would expect this outcome to occur with a non-trivial likelihood. It does not require high confidence that the outcome will definitely occur and excludes experiments in which an expert would anticipate the outcome to be technically possible, but highly unlikely."**

   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?**

At this time, we agree with defining "reasonably anticipated" as an outcome of concern that could occur with a non-trivial likelihood. While it is a reasonable definition for now, we suggest the federal government continue to better define this term with additional expert discussion.

5. **NSABB recommends the removal of blanket exclusions for research activities associated with surveillance and vaccine development or production for research with ePPPs (Recommendation 3).**

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

The Revised Policy should not contain exemptions for vaccine and surveillance work. The lack of wholesale exemptions would not prohibit vaccine or surveillance work with ePPPs from being proposed and reviewed and ultimately permitted by USG independent review. Exemptions for work with even distant relationship to vaccine science or surveillance create the potential for projects that pose a very high risk of epidemic or pandemic in the event of an accident or deliberate misuse to escape review. This would be the wrong decision for public benefit. Simply

put, benefits to vaccine or surveillance science should be considered in the benefit portion of the risk-benefit evaluation when ePPP work receives department-level review under the Revised Policy. If upon review the proposed ePPP work related to vaccine science or surveillance were judged to be important enough to do and the benefit outweighed the risks as determined by the USG independent review committee, then the work would be allowed to proceed. It will be important for those proposing work on the basis of vaccine science or surveillance to show a very clear connection to practical developments in those fields given the risks that could arise by the creation of novel ePPPs.

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

Broad exemptions for such work would create incentives to exaggerate the unique benefits of proposed work and deprecate the benefits of safer alternatives. There are examples of this exaggeration already in the literature. The recreation of the 1918 H1N1 influenza virus has been described by its authors as follows: "the benefits are obvious and manifold and have demonstrably contributed to the betterment of human health."[16] Yet careful analysis reveals that each of the public health benefits claimed arose either from the sequence (rather than the live virus) or from background biological knowledge. In other words, every one of the benefits could have been achieved without reconstructing the virus. Similarly, supporters of the H5N1 enhancement experiments have claimed benefits for surveillance and vaccine design,[17] notwithstanding that each mutation identified as important for transmission in those studies had been previously identified by a safer method not involving enhancement.[18]

Two of us have argued previously[19] that the relevant comparison when assessing benefits should be between a proposed ePPP experiment triggering enhanced review and expenditure of the same resources on alternative approaches to produce the same public health benefits (importantly, not necessarily through the same scientific knowledge). This is an appropriate comparison because researchers must make this decision: how best to achieve public health goals within an acceptable budget of cost and risk. It is also appropriate because it helps to resolve concerns about scientific freedom (much as the task for animal experiments is to reduce, refine, and replace) and about unanticipated benefits (which could come from the ePPP experiment but also from the alternative).

Important to note is that the speed of review under the Revised Policy is highly dependent on the level of resources the USG assigns to this process. If one of the values and commitments coming out of this Revised Policy review process is that the process should not slow down important scientific endeavors with clear benefits that outweigh the risks of an epidemic or pandemic from an accident or deliberate misuse, then the USG should apply sufficient program management and scientific resources to ensure the process can move quickly and transparently and strengthen over time with the publication of case studies, widespread education, and guidance.

[16] https://doi.org/10.1128/mbio.00201-12

[17] https://doi.org/10.1093/infdis/jiv473

[18] https://doi.org/10.1093/infdis/jiw348

[19] https://doi.org/10.1128/mbio.02366-14

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? For example, would vaccine research and development activities be unjustifiably impeded if the current P3CO policy framework exemption for "Activities associated with developing and producing vaccines, such as generation of high growth strains" was either removed completely or modified to "Research on PPPs directly associated with testing and/or producing vaccines, such as generation of high growth strains"?

There may be very specific, anticipated ePPP research or industrial process steps that the USG determines are so beneficial and understood that they are approved rapidly, and then used as a precedent. Presumably, that would generally be the case for the generation of high-growth strains for vaccines. But a complete exemption from the policy would not be appropriate, for example, if the generation of high-growth strains for flu vaccine would create large quantities of modified influenza virus that spreads more readily or causes more severe illness in humans. In such a case, it would be important for the USG to have approved of that process and assured that safety and security systems are sufficient. (We emphasize that we find it unlikely that high-growth strains used for vaccines would be those with enhanced transmissibility and use this only for illustration.) It is also clear that many or most of the approaches to vaccine development do not require the use of ePPP research.

6. NSABB recommends that continued assessment of the risks and benefits associated with advances and applications of bioinformatics, modeling, and other in silico experimental approaches and research involving genes from or encoding pathogens, toxins, or other agents must inform future evaluations of the scope of research oversight policies to help ensure that associated risks are appropriately identified and managed. (Recommendation 10.2). This type of research is not currently included in the DURC and ePPP oversight policies.

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?

We believe that it is premature to include bioinformatics, modeling, and other *in silico* experiments in the Revised Policy. However, we appreciate that "information hazards" generated by some *in silico* experiments pose risks and should ultimately be included in USG approaches to governing and overseeing DURC/ePPP research in the future. Work that generates information that enables the synthesis of novel ePPPs or other products of unusual public health consequence will require oversight. This is because publication of data and methods potentially could be used to synthesize and express ePPPs. However, there has not been sufficient time to understand and evaluate the nature of the most concerning types of information hazards, to evaluate the potential impact on ongoing work, or to leverage the help of IBCs that do not currently oversee *in silico* work, per se. While it is premature to broadly include this work under the Revised Policy, we urge the federal government, with the help of the NSABB, to more carefully evaluate this area and set a target for making governance and oversight recommendations in this increasingly important area of research.

b. One possible way to define this category of *in silico* research within a Revised Policy would be to include experiments that are reasonably anticipated to:

i. Develop *in silico* models that directly enable the predictive design of an enhanced potential pandemic pathogen or novel pathogen or toxin covered under a Revised Policy that could be constructed via genomic editing or de novo synthesis; and/or

ii. Develop a dataset(s) connecting nucleic acid or amino acid sequences with experimentally-determined pathogenic functions in a manner sufficient to enable the development of *in silico* models described in (i).”

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?

As stated above, it is premature at this time to include *in silico* models in the Revised Policy. Models, like other experimental tools, can be used for many purposes. It may be difficult to know *a priori* whether a model designed for one benign purpose will be used for a harmful purpose. Current discussion about today’s AI foundation models suggests that these models do not yet pose a risk of catastrophe in the form of creating a novel pathogen; however, many now anticipate that near-future AI models will pose such risks and will require a variety of risk mitigation measures.[20] The nature of these governance measures and how they should be implemented are not yet clear. In addition, inappropriate measures might have a perverse effect of discouraging the pursuit of less risky alternatives to some proposed ePPP research. We suggest that the USG closely monitor these developments and consider appropriate governance and oversight of AI models and AI-powered tools that generate clear risks of creating novel transmissible organisms.

[20] https://www-files.anthropic.com/production/files/responsible-scaling-policy-1.0.pdf

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