A Report of the National Science Advisory Board for Biosecurity

RECOMMENDATIONS FOR THE EVALUATION AND OVERSIGHT OF PROPOSED GAIN-OF-FUNCTION RESEARCH

May 2016

Contents

List of Acronyms

Bioethics Commission	Presidential Commission for the Study of Bioethical Issues
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSAT	biological select agents and toxins
BSL	biosafety level
CDC	Centers for Disease Control and Prevention
CoV	coronavirus
DURC	dual use research of concern
FBI	Federal Bureau of Investigation
FDA	Food and Drug Administration
FESAP	Federal Experts Security Advisory Panel
FSAP	Federal Select Agent Program
FTAC-SAR	Fast Track Action Committee on Select Agent Regulations
GOF	gain-of-function
GOFROC	gain-of-function research of concern
HHS	Department of Health and Human Services
HHS Framework	Framework for Guiding U.S. Department of Health and Human Services Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets
HPAI	highly pathogenic avian influenza
IBC	Institutional Biosafety Committee
LPAI	low pathogenic avian influenza
MCM	medical countermeasures
MERS	Middle East Respiratory Syndrome
National Academies	National Academies of Sciences, Engineering, and Medicine
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIH Guidelines	NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules
NSABB	National Science Advisory Board for Biosecurity
RAC	Recombinant DNA Advisory Committee
RBA	risk and benefit assessments
SARS	Severe Acute Respiratory Syndrome
USDA	U.S. Department of Agriculture
USG	U.S. Government

Executive Summary

Research involving pathogens is essential to global health and security. Such research provides insight into the fundamental nature of human-pathogen interactions, enables the assessment of the pandemic potential of emerging infectious agents, and informs public health and preparedness efforts, including the development of medical countermeasures. Several federal policies are in place to help ensure that pathogen research is conducted safely and in ways that minimize the risks of laboratory accidents and security risks. A number of biosafety incidents at Federal facilities in 2014 prompted renewed efforts to promote and enhance biosafety and biosecurity. Concerns were also raised about certain "gain-of-function" (GOF) studies with the potential to generate pathogens with pandemic potential. The concerns centered on whether a pathogen with enhanced transmissibility and/or virulence could be accidentally or intentionally released from a laboratory, potentially exposing surrounding populations and possibly causing a wider pandemic.

The U.S. government (USG), as part of its continued focus on biosafety and biosecurity, undertook a deliberative process to carefully examine the risks and benefits associated with certain GOF studies. The deliberative process involved the National Science Advisory Board for Biosecurity (NSABB), which was tasked with making recommendations to the USG on this topic, and the National Academies of Sciences, Engineering, and Medicine (National Academies), which was tasked to convene two public symposia to generate broad discussion on relevant issues. To further inform NSABB deliberations, the National Institutes of Health (NIH) commissioned two studies – an independent assessment of the risks and benefits associated with GOF studies, conducted by Gryphon Scientific, and an ethical analysis of the issues related to funding and conducting such studies, performed by Professor Michael Selgelid.

The NSABB was charged with advising on the design of the risk and benefit assessments (RBA) for GOF studies and with providing recommendations to the USG on a conceptual approach for evaluating proposed GOF studies. In May 2015 the NSABB issued its *Framework for Guiding the Conduct of Risk and Benefit Assessments of Gain-of-Function Research*, which guided NIH in overseeing the contractor conducting the RBA. In May 2016, informed by the results of the RBA as well as its analysis of the current policy landscape, consideration of relevant ethical issues, and consultations with domestic and international stakeholders, the NSABB finalized the report that follows – *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research* – which describes the Board's analyses and findings, and articulates its recommendations to the USG for the evaluation and oversight of proposed GOF studies.

NSABB Findings:

Finding 1. There are many types of GOF studies and not all of them have the same level of risks. Only a small subset of GOF research—GOF research of concern (GOFROC)—entail risks that are potentially significant enough to warrant additional oversight.

Finding 2. The U.S. government has several policies in place for identifying and managing risks associated with life sciences research. There are several points throughout the research life cycle where, if the policies are implemented effectively, risks can be managed and oversight of GOF research of concern could be implemented.

Finding 3. Oversight policies vary in scope and applicability, and do not cover all potential GOFROC, therefore, current oversight is not sufficient for all GOF research of concern.

Finding 4. An adaptive policy approach is a desirable way to ensure that oversight and risk mitigation measures remain commensurate with the risks associated with the research and that the benefits of the research are being fully realized.

Finding 5. There are life sciences research studies, including possibly some GOF research of concern, that should not be conducted because the potential risks associated with the study are not justified by the potential benefits. Decisions about whether specific GOFROC should be permitted will entail an assessment of the potential risks and anticipated benefits associated with the individual experiment in question. The scientific merit of a study is a central consideration during the review of proposed studies but other considerations, including legal, ethical, public health, and societal values are also important and need to be taken into account.

Finding 6. Managing risks associated with GOF research of concern, like all life sciences research, requires both federal and institutional oversight, awareness and compliance, and a commitment by all stakeholders to safety and security.

Finding 7. Funding and conducting GOF research of concern encompasses many issues that are international in nature.

NSABB Recommendations to the U.S. government:

Recommendation 1. Research proposals involving GOF research of concern entail significant potential risks and should receive an additional, multidisciplinary review, prior to determining whether they are acceptable for funding. If funded, such projects should be subject to ongoing oversight at the federal and institutional levels.

As part of this recommendation, the NSABB has proposed a conceptual approach for guiding funding decisions about GOFROC. First, the NSABB identified the attributes of GOFROC, which is research that could generate a pathogen that is: 1) highly transmissible and likely capable of wide and uncontrollable spread in human populations; and 2) highly virulent and likely to cause significant morbidity and/or mortality in humans. Next, the NSABB identified a set of principles that should guide funding decisions for GOFROC. Only research that is determined to be in line with these principles should be funded. Additional risk mitigation measures may be required for certain research studies to be deemed acceptable for funding.

Recommendation 2. An advisory body that is designed for transparency and public engagement should be utilized as part of the U.S. government's ongoing evaluation of oversight policies for GOF research of concern.

Recommendation 3. The U.S. government should pursue an adaptive policy approach to help ensure that oversight remains commensurate with the risks associated with the GOF research of concern.

> **Recommendation 3.1.** The U.S. government should develop a system to collect and analyze data about laboratory safety incidents, near-misses, and security breaches as well as the effectiveness of mitigation measures to inform GOF research of concern policy development over time.
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> **Recommendation 3.2.** The U.S. government should develop or facilitate the development of a system to collect and analyze data about Institutional Review Entity (IRE) challenges, decisions, and lessons learned to provide feedback to the IRE community and to inform policy development for GOF research of concern over time.

Recommendation 4. In general, oversight mechanisms for GOF research of concern should be incorporated into existing policy frameworks when possible.

Recommendation 5. The U.S. government should consider ways to ensure that all GOF research of concern conducted within the U.S. or by U.S. companies be subject to oversight, regardless of funding source.

Recommendation 6. The U.S. government should undertake broad efforts to strengthen laboratory biosafety and biosecurity and, as part of these efforts, seek to raise awareness about the specific issues associated with GOF research of concern.

Recommendation 7. The U.S. government should engage the international community in a dialogue about the oversight and responsible conduct of GOF research of concern.

1. Introduction

A robust life sciences research enterprise is necessary to counter the continually evolving threats to public health and national security posed by endemic and emerging pathogens, as well as malicious biological threats. By helping to define the nature of human-pathogen interactions, life sciences research promotes public health and national security not only by enhancing our understanding of pathogen biology and disease pathogenesis, but also by informing biosurveillance and medical countermeasure development. Such research can also aid in the assessment of the pandemic potential of emerging infectious agents, thereby underpinning health policy decisions and preparedness and response efforts.

While the ultimate goal of life sciences research involving pathogens is the protection and promotion of public health, there are inherent associated biosafety and biosecurity risks. Potential risks might arise from laboratory accidents or security breaches that result in laboratory acquired infections or the accidental or deliberate release of a pathogen from containment. Life sciences research also has "dual use" potential. That is, legitimate research may generate information, products, or technologies that could be misused to threaten public health or national security. To mitigate such dual use concerns, as well as potential biosafety and biosecurity risks, research involving pathogens is subject to multiple layers of federal and institutional oversight.

The Gain-of-Function Debate and the U.S. Government Response

Experimental techniques and approaches that modify microorganisms are routinely employed in pathogen research to ascertain the roles of genes and their functional products. Such studies are fundamental to the field of microbiology and facilitate correlation of genetic and phenotypic characteristics – a critical step in deciphering the complex nature of host-pathogen interactions that underlie transmission, infection, and pathogenesis. Such manipulations can result in either diminished (loss-of-function) or enhanced (gain-of-function) biological phenotypes (see Box 1).

Studies that result in the generation of pathogens with enhanced, or gain-of-function (GOF), phenotypes are conducted for a number of valid scientific purposes. Such studies provide information that adds to the scientific knowledge base and can inform biosurveillance, medical countermeasure development, and public policy decision-making related to public health and preparedness. The vast majority of such GOF studies do not raise significant safety or security concerns. However, certain GOF studies involving pathogens have raised concerns about whether a laboratory-generated pathogen with pandemic potential could be accidentally or intentionally released, resulting in significant consequences to public, or perhaps, global health. Concerns have also been raised about whether certain GOF studies could generate information that could enable individuals with malevolent intent to generate a pathogen with pandemic potential.

The controversy over certain GOF studies arose after two groups demonstrated that highly pathogenic avian influenza H5N1 viruses with a small number of experimentally-induced mutations became transmissible between mammals by respiratory droplets.[1,2] In 2012, in response to the controversy associated with publication of the manuscripts describing these findings, the influenza community initiated a voluntary suspension of certain GOF studies involving highly pathogenic avian influenza H5N1 viruses. During that time, policymakers considered whether certain GOF studies should be conducted using federal funds, and if so, how those studies could be safely conducted. The Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) issued new biosafety guidelines for working with highly pathogenic avian influenza strains.[3,4] The U.S. Department of Health and Human Services (HHS) developed a framework for guiding its funding decisions about GOF projects that may generate H5N1 or H7N9 avian influenza viruses that are transmissible between mammals by respiratory droplets.[5,6]

Concerns regarding laboratory safety and biosecurity were renewed following a number of biosafety incidents at U.S. Federal laboratories reported during the summer of 2014. The incidents did not involve GOF studies *per se* but raised broader concerns about laboratory safety and security as it applies to pathogen research.

Box 1. Gain-of-Function Research

Recently, the phrase "gain-of-function research" has become synonymous with certain studies that enhance the ability of pathogens to cause disease. However, gain-of-function studies, as well as loss-of-function studies, are common in molecular microbiology and are essential to understanding molecular pathogenesis of infectious diseases. Changes to the genome of an organism, whether naturally occurring or directed through experimental manipulations in the laboratory, can result in altered phenotypes, as biological functions are lost or gained. Investigators routinely conduct loss- and gain-of-function experiments to understand the complex nature of host-pathogen interactions that underlie transmission, infection, and pathogenesis.

The term "gain-of-function" is generally used to refer to changes resulting in the acquisition of new, or an enhancement of existing, biological phenotypes. This report further defines "gain-of-function research of concern" to describe the subset of studies that have been the subject of recent debate and have raised potential biosafety and biosecurity implications. These are gain-of-function studies with the potential to generate pathogens with pandemic potential in humans by exhibiting high transmissibility and high virulence. See Section 6 for a more rigorous description of GOF research of concern (GOFROC).

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[1] Imai, M., et al. *Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets*. Nature 486, 21 June 2012.

[2] Herfst, S., et al. *Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets*. *Science* 336, 22 June 2012.

[3] Gangadharan, D., Smith, J., and Weyant, R., *Biosafety Recommendations for Work with Influenza Viruses Containing a Hemagglutinin from the A/goose/Guangdong/1/96 Lineage*. Morbidity and Mortality Weekly Report 62(RR06); 1-7. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6206a1.htm

[4] *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*. http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines

[5] *Framework for Guiding Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets*. February 21, 2013. http://www.phe.gov/s3/dualuse/Documents/funding-hpai-h5n1.pdf

[6] Jaffe, H.W., et al. *Avian flu: Extra Oversight for H7N9 Experiments*. Nature 500, 8 August 2013. http://www.nature.com/nature/journal/v500/n7461/full/500151a.html

As one component of comprehensive efforts to review and enhance laboratory biosafety and biosecurity, the U.S. government (USG) embarked on a deliberative process to re-evaluate the risks and benefits of certain GOF research with a goal of developing policy governing the funding and conduct of such research.[7] The deliberative process involved the National Science Advisory Board for Biosecurity (NSABB), which served as the official federal advisory body for providing advice in this area, and the National Academies of Sciences, Engineering, and Medicine (National Academies), which fostered broader scientific and public discussions on the topics. To inform NSABB deliberations, NIH commissioned formal risk and benefit assessments (RBA) of GOF research involving pathogens with pandemic potential and a separate analysis of ethical issues surrounding the conduct of such studies. Stakeholder input was also essential to the process.

The deliberative process was accompanied by a pause in the provision of new federal funds for certain GOF research involving influenza, Middle East Respiratory Syndrome (MERS) or Severe Acute Respiratory Syndrome (SARS) viruses—pathogens determined to have pandemic potential. Specifically:

> *New USG funding will not be released for gain-of-function research projects that may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. This restriction would not apply to characterization or testing of naturally occurring influenza, MERS, and SARS viruses, unless the tests are reasonably anticipated to increase transmissibility and/or pathogenicity.*[8]

In parallel, the USG encouraged the research community (both those who receive USG funding and those who do not) to join in adopting a voluntary pause on any ongoing research that involves the types of studies that are subject to the funding restriction above.

NSABB recommendations conveyed in this report will inform the USG as it develops policy about whether certain types of GOF studies on pathogens with pandemic potential should be supported and, if so, how such research proposals should be evaluated to inform funding and oversight decisions. It is expected that the temporary funding pause will be lifted and/or replaced by a decision or policy that addresses GOF research involving the generation of pathogens with pandemic potential.

[7] *United States Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses*. U.S. Government, October 17, 2014. http://www.phe.gov/s3/dualuse/documents/gain-of-function.pdf

[8] Ibid.

2. NSABB Charge

On October 22, 2014, as part of the USG's deliberative process for GOF studies, the NSABB was issued its charge to:

1. Advise on the design, development, and conduct of risk and benefit assessments for GOF studies, and
2. Provide recommendations to the U.S. government on a conceptual approach to the evaluation of proposed GOF studies

In developing its recommendations the NSABB was asked to consider: the results of the risk and benefit assessments; the discussions hosted by the National Academies; the spectrum of potential risks and benefits associated with GOF studies; and any alternative methods that may be employed to yield similar scientific insights or benefits, while reducing potential risks.

Since gain-of-function studies encompass a broad spectrum of pathogens and experimental manipulations, the NSABB discussed its charge and sought to identify the appropriate scope for its deliberations. Since the experiments that initiated the controversy involved the generation of pathogens that were concerning from a human health perspective, NSABB deliberations and recommendations focus on pathogens that pose risks to human populations. NSABB recommendations also focus on guiding USG funding decisions but the Board also considered issues associated with non-federally funded research and international research.

3. NSABB Deliberative Approach

The deliberative process (Figure 1) initiated by the USG to evaluate the risks and benefits of GOF studies involved the NSABB and the National Academies. To address its charge, NSABB formed two working groups to develop draft recommendations, which were then discussed by the full Board[9]. The National Academies convened public forums to stimulate broad discussions and receive additional stakeholder input. The first forum was held early in the deliberative process and a second was held in March 2016; both were designed to inform NSABB deliberations.

To inform the deliberative process further, NIH commissioned two additional analyses: 1) qualitative and quantitative risk and benefit assessments of GOF research, conducted by Gryphon Scientific, and 2) a review of the ethical considerations associated with the GOF issue and an analysis of relevant ethical decision-making frameworks, conducted by Dr. Michael Selgelid.

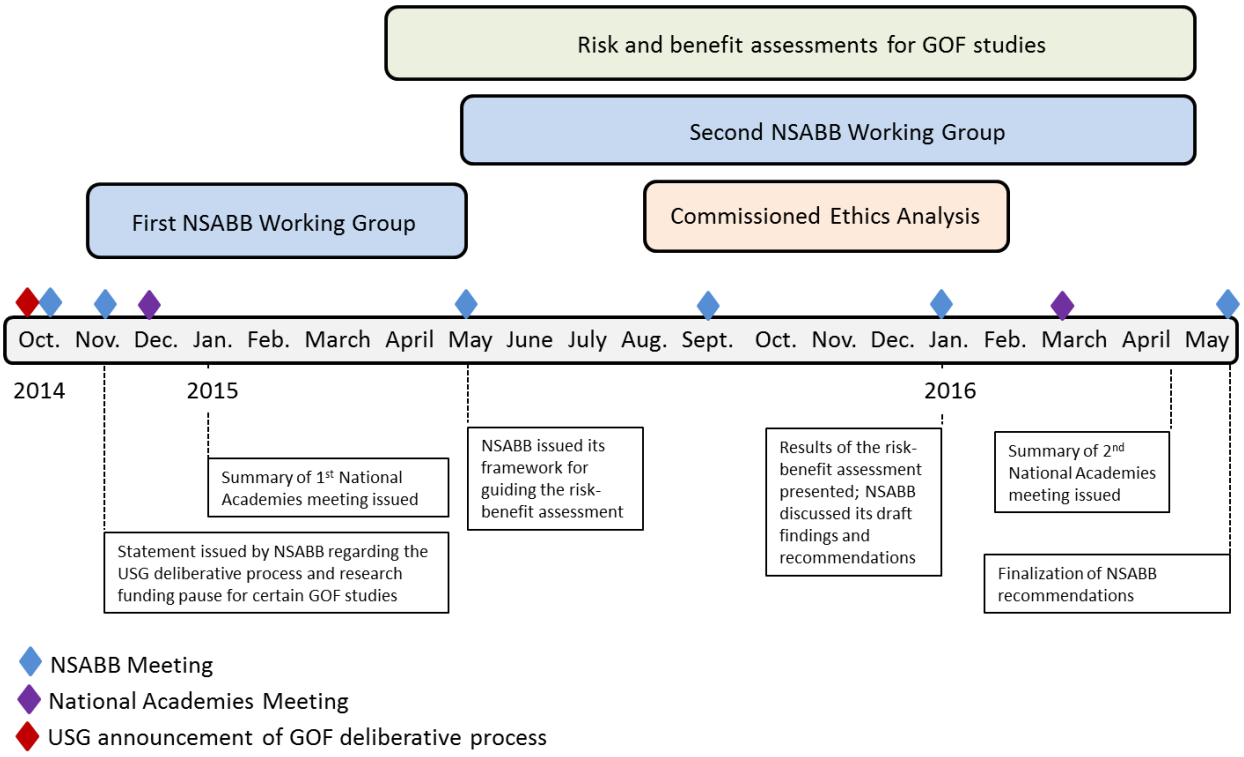

Figure 1. Timeline and major events of the GOF deliberative process.

[9] Information about these meetings and activities, including agendas, summaries, and archived videocasts, can be found on the NSABB website at: http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/nsabb/nsabb-meetings-and-conferences/past-meetings

The NIH Office of Science Policy, which administers the NSABB, managed the overall deliberative process. NIH oversaw the work of its contractors, Gryphon Scientific and Dr. Michael Selgelid, and interfaced between the NSABB and contracted entities.

More information regarding the process and NSABB deliberations may be found in Appendices. Appendix A provides a detailed description of the NSABB's deliberative approach. Appendix B summarizes the current U.S. policy landscape for the oversight of pathogen research. Appendix C describes examples of studies that would or would not be considered GOF research of concern. Appendix D provides an overview of stakeholder views that were presented and considered by NSABB. Appendix E lists the experts and sources consulted by NSABB, including those who submitted public comments. Appendix F and G list the NSABB roster and charter. NSABB's *Framework for Guiding the Conduct of Risk and Benefit Assessments of Gain-of-Function Research*, which was approved by the Board in May 2015, is provided in Appendix H.

Guiding Principles for NSABB Deliberations

Early in the overall process the NSABB developed the principles below to guide its deliberations and underpin its analysis of the risk and benefit assessments.

1. The NSABB deliberations should focus on defining the GOF problem then include broad consideration of possible solutions. A range of approaches and decision-making frameworks will be considered, and the NSABB will take into account these various approaches when developing its recommendations.

2. NSABB will consider the potential risks and benefits of a broad range of GOF studies involving influenza, SARS, and MERS viruses in order to identify those that may raise significant concerns that should be addressed. However, the NSABB will aim to develop recommendations that are grounded in broadly-applicable concepts and principles that could, if necessary, apply to GOF studies involving other pathogens that may require evaluation in the future.

3. Similarly, NSABB will consider the risks and benefits associated with alternative research approaches to GOF research to understand whether or not these may substitute for or complement GOF studies.

4. NSABB recommendations will be informed by data and information about potential risks and benefits as well as values that will guide the evaluation and comparison of these risks and benefits. Ethical, societal, and legal considerations will also contribute to the development of recommendations and these inputs should be explicitly identified, discussed, and prioritized.

5. NSABB recognizes that not all analyses relevant to its task are quantitative and that uncertainties inherent in any quantitative analysis may remain. NSABB will seek to document important areas of uncertainty in any data or analysis when necessary.

6. NSABB should publicly debate its draft recommendations and describe in its report any dissenting views that may vary substantially from the Board's recommendations.

7. NSABB should consider current USG policies and guidelines, determine whether they adequately address risks associated with GOF research (in light of potential benefits), and make recommendations that are consistent with that determination. Current policies may be adequate or require only minor changes; alternatively, significant enhancements may be needed. The adequacy of current policy to cover GOF studies may vary by pathogen. Recognizing the paramount importance of ensuring safety, security, and public health, policies should also minimize the burdens placed upon the conduct of science.

8. NSABB recommendations will inform the development of U.S. government policy, which will apply to research funded, conducted, or overseen by the U.S. government either domestically or internationally. NSABB will be mindful in its deliberations of the likelihood that the Board's recommendations and U.S. policy decisions will also influence other governments and non-USG funders of life sciences research.

9. The NSABB will also consider whether there are certain studies that should not be conducted under any circumstances, and if so, articulate the critical characteristics of such studies.

10. Maintaining public trust and confidence in life sciences research is critical and must be taken into account as recommendations are formulated.

4. Analysis

In developing recommendations on a conceptual approach for evaluating GOF proposals, NSABB examined three major areas: the current policy landscape for overseeing research involving pathogens, the ethical issues associated with funding and conducting GOF studies, and the results of the risk and benefit assessments of GOF research. In addition, the NSABB considered broad stakeholder perspectives through presentations from domestic and international experts at working group and full NSABB meetings, analysis of published articles, and comments from attendees at NSABB meetings or public comments submitted to the Board.

4.1. Analysis and Interpretation of the Risk and Benefit Assessment

The NSABB reviewed the risk and benefit assessments conducted by Gryphon Scientific, which were designed to evaluate the risks and benefits of GOF research in a manner that encompassed both benign and worrisome aspects of a broader range of GOF studies than those that have raised concerns. The RBA analyzed biosafety and biosecurity risks as well as possible benefits. Overall, the RBA includes a commendable amount of sophisticated work and analysis, is generally well-done, and largely achieves the goals it was intended to address. Gryphon's draft RBA report was made publically available in December 2015 and key results were presented and discussed at NSABB and National Academies meetings. The final report was issued in April 2016 and is available on Gryphon's website.[10]

Strengths of the Risk and Benefit Assessments

The RBA has significant strengths. It is a thorough and extensive analysis of the risks and benefits of GOF work in the context of the guidance provided in the NSABB *Framework for Conducting Risk and Benefits Assessments of Gain-of-Function Research*.[11] It takes into account the principles articulated in the framework and includes the agents, categories of possible risks, types of possible benefits, and possibly concerning scenarios and phenotypes that were laid out in the *Framework*. It was agreed that a few items from the *Framework* not be analyzed or focused on in the RBA so that the most probable issues of concern could be thoroughly addressed within the available time and resources.[12]

The biosafety risk assessment does a credible job of defining the relative risks associated with potential laboratory accidents involving GOF manipulations of pathogens with enhanced characteristics as compared to wild-type pathogens. This analysis is performed in a semi-quantitative way; it uses

[10] *Risk and Benefit Analysis of Gain-of-Function Research, Final Report*. Gryphon Scientific, April 2016. http://www.gryphonscientific.com/wp-content/uploads/2016/04/Risk-and-Benefit-Analysis-of-Gain-of-Function-Research-Final-Report.pdf

[11] *Framework for Conducting Risk and Benefits Assessments of Gain-of-Function Research.* National Science Advisory Board for Biosecurity, May 2015. http://osp.od.nih.gov/sites/default/files/resources/NSABB_Framework_for_Risk_and_Benefit_Assessments_of_GOF_Research-APPROVED.pdf

[12] National Science Advisory Board for Biosecurity Meeting, May 5, 2015. http://osp.od.nih.gov/office-biotechnology-activities/event/2015-05-05-120000-2015-05-05-200000/national-science-advisory-board-biosecurity-nsabb-meeting

appropriate, established, peer-reviewed methods to the extent available. The parametric approach employed is powerful and allows consideration of many situations of interest.

The report effectively illustrates that the harmful events being modeled are low probability (see Figures 6.2 and 6.4 in Gryphon's report). Only a small fraction of laboratory accidents would result in a loss of containment. Of those, only a small fraction would result in a laboratory acquired infection, and of those, only a fraction would spread throughout the surrounding community (or to the global population). The NSABB recognizes the challenge of analyzing low-probability, high-consequence events for which little data exists and appreciated attempts to make this point clear in the RBA.

The biosecurity risk assessment is primarily qualitative, and highlights analysis of previous malevolent events and evasions of security systems, likely capabilities and motivations of various possible actors, and an evaluation of the systems in place to prevent biosecurity breaches. Information was obtained from a survey of literature and discussions with biosecurity, intelligence, and law enforcement professionals. It is an extensive gathering of a wide range of information that has not been presented before in one place.

The information risk assessment (an element of the biosecurity risk assessment) is a qualitative analysis of risks that may result from the misuse of information derived from certain GOF studies that might be published in the future. It identifies information that might be attractive to malicious actors and compares it to other sources of information they might find attractive.

The benefits assessment uses a novel approach to assess potential benefits of GOF studies, a difficult task with little prior methodology to draw upon. The results are not quantitative, and attempts at quantification would have been appreciated. However, as is, the assessment may be the best that can be done with the available information and analytic tools. The benefits assessment thoroughly analyzes the possible benefits of alternatives to GOF studies and identifies areas where GOF research appears to provide unique benefits (i.e., benefits that are not attainable without the use of GOF), either currently or in the near future.

The RBA contains a number of other useful analyses as well, including background and contextual information on the biology of influenza and coronavirus, historical analysis of naturally-occurring seasonal and pandemic influenza and coronavirus outbreaks, an examination of the potential proliferation of GOF research, and analysis of the potential loss of public trust in science that could result if a laboratory incident involving GOF research were to occur. Significantly, the historical analysis notes that each year, influenza infects 5 – 10% of the world's population, resulting in significant morbidity and mortality (up to 500,000 deaths per year). This description of naturally-occurring influenza (and coronavirus) infections helps to establish the extant risks associated with these infectious diseases to which the risks associated with GOF studies might be compared.

Overall, the RBA is comprehensive, objective, reasonable, and generally extensively documented.

Limitations of the Risk and Benefit Assessments

The RBA also has some weaknesses and limitations that should be noted. First, the RBA was limited to the types of labs traditionally funded by the Federal government, which may not be representative of other settings where GOF research may be conducted. Every attempt was made to base the analyses in the RBA on scientific information and data. Nevertheless, data on the properties of the various pathogens being examined, events such as laboratory accidents or security breaches, or possible future acts of terrorism, are limited in some cases and unavailable in principle in others. Therefore, assumptions and estimations were necessary. For this reason, the biosafety risk assessment is not fully quantitative, primarily because absolute, quantitative baselines for the risk of work with wild-type pathogens could not be estimated with any certainty. Thus, the data presented are primarily comparative, and provide relative, rather than absolute, values for the risks associated with laboratory accidents involving GOF studies.

Gryphon compared the risks associated with potential lab accidents involving a GOF strain with the risks associated with the same accident involving a wild-type strain. This comparative approach is adequate for some scenarios but inadequate for others. For example, an increased risk associated with a GOF study that is relatively large (5-10-fold or greater) may appear significant, but if this increase is in comparison to a very small risk baseline, the overall risk associated with the GOF study may not be significant or concerning. Similarly, small increases in risk over a higher risk baseline, in fact, may be concerning. Additionally, differences in risk that are relatively small (about 2-fold) are difficult to interpret because such changes may fall within the limits of uncertainty for the analysis. Attempts to include some absolute baseline estimates of risk (an admittedly difficult task) were included in Section 6.8 of Gryphon's report. However, the lack of comprehensive estimates of baseline risk make interpreting the biosafety risks a challenge.

Given the comparative approach undertaken for the biosafety risk assessment, the implications of the results of this analysis depend a great deal on the wild-type comparator strains that were selected for the analysis. For instance, for pandemic influenza Gryphon initially selected the 1918 influenza strain as the comparator. Gryphon regarded this strain as embodying the maximum risk for influenza, yet a level of risk that is also deemed as acceptable given that research with this strain is permitted. However, using 1918 influenza as the comparator for the analysis compares GOF risks to a relatively high level of baseline risk, making the changes in risk associated with GOF manipulations comparatively small. Utilizing different comparator strains alters the relative risks associated with GOF manipulations. Using a high-risk baseline strain may obscure significant risks associated with GOF studies whereas using a strain with a low risk baseline may inflate the potential risks associated with GOF studies.

Little data exists about the probabilities of the accidents that initiate the chain of events that may lead to a pandemic and therefore, the quantitative probability of these accidents could not be incorporated into the biosafety risk assessment. The modeling of secondary spread of a pathogen through populations once it is released from a laboratory allows for some estimation of the consequences of an event, but without a better understanding of the likelihood that an accident would result in loss of containment or a laboratory acquired infection it is difficult to make judgments about the overall risk.

Gryphon's analysis accounts for this by presenting relative, actuarial risk. However, this approach results in the challenges associated with comparing relative risks described above. There are large uncertainties in most of the input parameters that are the basis for the biosafety risk calculations. Uncertainties about inferring absolute risk from these relative risks exist and were kept in mind as the Board developed its findings and recommendations.

The biosecurity risk assessment attempts to examine how GOF studies add to the risk of malevolent acts. Portions of the biosecurity risk assessment focus on GOF studies but others describe the type of threats that could occur against any high-containment laboratory. The semi-quantitative portion of the biosecurity risk assessment estimates probabilities for escape and secondary spread and escape from local control for various pathogens and event types. However, this analysis (see section 7.4 and Table 7.7 in Gryphon's report) assumes that 1, 5, or 10 individuals are initially infected as a result of a malicious act with no indication of how likely such an event would be, since there is no way to make such an estimate.

While exhaustively documented, the RBA is not always transparent about data reliability. In particular, interviews were used to gather much critical information, and this was not always well documented in a way that reflects how robust the resulting information may be. For peer-reviewed publications, this is less of a concern.

While evaluation of the benefits of alternatives to GOF studies is extensive, evaluation of risks of alternative approaches is not as thorough. In addition, risks and benefits are not presented in comparable terms, making it a challenge to determine whether certain risks are justified by potential benefits. Significantly, the benefit assessment is not quantitative and there is no probability analysis or attempt to estimate the likelihood that a certain benefit would be realized or what its impact might be.

Key Results of the Risk and Benefit Assessments

While NSABB considered all of the analyses in the RBA, some results are important to highlight. In general, the RBA examined risks and benefits associated with the major GOF phenotypes with the intention of identifying types of studies that would be most and least concerning, based particularly on their risk profile.

With regard to biosafety risks, only some potential GOF phenotypes represent substantially increased (5- to 10-fold or more) risks over the starting strain. Two-fold changes most likely fall within the uncertainty of the data, and while small differences might be important if it could be shown that they are significant, this demonstration is probably difficult. For coronaviruses, GOF studies that would create strains with increased transmissibility among mammals may entail significant risks if they also increase human transmission. The risks, were this combination to occur, would include increased probability of an outbreak escaping local control and increased likelihood of global consequences. In addition, experiments that enhance coronavirus growth in culture would likely increase the possibility of laboratory acquired infections.

For seasonal influenza, the GOF phenotypes entailing the greatest risks include enhanced transmission in mammals (assuming this increases transmission in humans), enhanced virulence, and evasion of immunity. Enhanced pathogenicity might significantly increase the global consequences of an outbreak.

For pandemic influenza, the issue of what GOF phenotypes could increase risk is highly dependent on the comparator strain used. If 1918 influenza is modified so that it is able to evade residual immunity, it could become more of a threat than 1957 H2N2, the comparator Gryphon used. For 1957 H2N2, enhancement of pathogenicity to that of 1918 also significantly increases risk. Other phenotype changes had little effect. However, if less transmissible and/or less virulent pandemic strains were used as the basis for comparison, the risks of some other GOF studies would appear to increase risk more significantly.

For avian influenza, the GOF experiments that lead to enhanced transmissibility in mammals (and presumably humans) would likely lead to an increased probability of local and widespread outbreaks, as well as increased global consequences. More subtle aspects of these very general conclusions may be found in the biosafety risk section and the Executive Summary of Gryphon's RBA report.

In general, GOF studies that were not considered by the NSABB to entail significant risks were those that would: adapt human pathogens to mammals to generate animal models; enhance the growth of attenuated vaccine strains; and antigenic drift studies that are commonly used to guide vaccine selection.

The biosecurity risk assessment shows that the most probable threats involve insiders who have direct access to dangerous pathogens or outsiders who collaborate with or subvert insiders. If currently mandated biosecurity systems are effective, outsiders have little chance of causing harm on their own. The RBA report also concludes that the risks associated with information from future GOF studies with influenza, SARS or MERS appear small; this is because most of the information of interest is already published, or non-GOF information relating to pathogens that are more attractive to individuals with malevolent intent is readily available. However, future scientific advancements could alter this assessment.

Most GOF studies provide benefits in the form of new scientific knowledge, and some of these benefits are unique (i.e., unable to be achieved by alternative, non-GOF approaches). While some GOF studies are likely to provide unique near-term benefits, these are associated with specific agents and phenotypes. With regard to more applied benefits, such as countermeasure development and biosurveillance, the most clear-cut example is experiments that increase growth of seasonal influenza vaccine candidates in culture. These studies provide unique benefits to current production of seasonal influenza vaccines, and likely will in the future. Another reasonably clear unique benefit is derived from experiments that enhance mammalian pathogenicity of coronaviruses as a means of developing animal models for studying disease and developing countermeasures. GOF studies that yield phenotypes that provide unique benefits to countermeasure development include enhanced pathogenicity, evasion of vaccines, and evasion of therapeutics. For several other potential benefits of GOF studies involving seasonal influenza, either the potential benefit is long term, or alternative approaches may yield the

same or similar benefits. Interestingly, few unique benefits pertaining to GOF studies involving pandemic influenza were identified. There are several types of GOF studies that entail generating avian influenza strains with phenotypes that may be valuable for surveillance and preparedness efforts, although other advances are needed to fully realize such benefits. This point is controversial, with strong proponents and critics. Additionally, a variety of benefits of GOF studies were identified that may also be provided to some extent by alternative approaches. It should be noted that no attempt was made to provide a probability assessment based on historical data for potential benefits; hence no direct comparison of risk to benefit for a proposed research project is possible.

4.2. Consideration of Ethical Values

The RBA provides information about the potential risks and benefits associated with conducting GOF research, however, determinations about whether such studies should be undertaken involve value judgments based on weighing the risks and benefits. The NSABB identified a number of values that are applicable to the decisions about whether to fund certain GOF studies and how to oversee them. Sources of these values include the Belmont Report,[13] the literature on public health ethics,[14] and the literature on oversight of emerging technologies,[15] as well as the literature specifically debating appropriate approaches to overseeing dual use research of concern (DURC) and GOF research that has raised concerns.[16,17,18,19,20] The commissioned ethics analysis conducted by Dr. Michael Selgelid describes additional values as well as decision-making frameworks to be considered.[21]

Substantive values

The following values are important to consider when determining whether to fund a research proposal involving GOF studies that might entail significant risks.

Non-maleficence: not causing harm. There are inherent risks associated with research involving pathogens that could result in harm to individuals as a result of accidental or intentional infection

[13] The Belmont Report. Office of the Secretary, U.S. Department of Health and Human Services. *Ethical Principles and Guidelines for the Protection of Human Subjects Research*. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979. http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

[14] Kass, N.E., *An Ethics Framework for Public Health*. American Journal of Public Health. 2001; 91(11):1776-1782. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1446875/

[15] *New Directions. The Ethics of Synthetic Biology and Emerging Technologies*. Presidential Commission for the Study of Bioethical Issues, December 2010. http://bioethics.gov/sites/default/files/PCSBI-Synthetic-Biology-Report-12.16.10_0.pdf

[16] Resnik, D.B., *H5N1 Avian flu research and the ethics of knowledge*. Hastings Center Report 2013; 43, 2: 22-33.

[17] Kelle, A., *Beyond patchwork precaution in the dual-use governance of synthetic biology*. Sci Eng Ethics. 2013 Sep; 19(3):1121-39.

[18] Kuhlau, F., Höglund, A.T., Evers, K., Eriksson, S., *A precautionary principle for dual use research in the life sciences*. Bioethics. 2011 Jan; 25(1):1-8.

[19] *Biotechnology Research in the Age of Terrorism*. The National Academies, 2004. http://www.nap.edu/catalog/10827/biotechnology-research-in-an-age-of-terrorism

[20] *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information*. National Science Advisory Board for Biosecurity, June 2007. http://osp.od.nih.gov/sites/default/files/resources/Framework%20for%20transmittal%20duplex%209-10-07.pdf

[21] Selgelid, M., *Gain-of-Function Research: Ethical Analysis*. April 2016. http://osp.od.nih.gov/sites/default/files/Gain_of_Function_Research_Ethical_Analysis.pdf

with the pathogen. These might include: causing disease; loss of lives; damage to the economy, national or international security, or agriculture; or loss of public trust in science or governance structures. Approaches aimed at preventing harm and mitigating potential risks should be considered and applied to the design, conduct, and communication of GOF research involving pathogens.

Beneficence: promoting beneficial outcomes while preventing harmful outcomes; appropriately balancing benefits and risks; formulating policy that maximizes public benefit while minimizing public harm. Benefits might include: preventing disease; saving lives; improving public health; enhancing the economy, national and international security, or public trust in science and governance structures. When the ultimate goals of the research are to improve public health, public health ethics would consider how effective the research is likely to be in achieving those goals, what the known or potential burdens of the research are, whether those burdens can be minimized, whether there are alternative approaches that are less risky or burdensome, and how the potential benefits and burdens of the research can be fairly balanced. The work of the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) suggests that those formulating and implementing government policy on scientific research and emerging technologies have a duty of public beneficence – a duty "to promote individual activities and institutional practices…that have great potential to improve the public's well-being," while being "vigilant about risks and harms, [and] standing ready to revise policies that pursue potential benefits with insufficient caution."[22] Both risks and benefits have associated probabilities, magnitudes, and uncertainties. In some instances, it may be justifiable to pursue benefits despite the potential risks; in others, the potential benefits may be foregone due to possible risks.

Social justice: distributing potential benefits and harms fairly (distributive justice) and selecting participants in research fairly, as well as those who may potentially be exposed to risk. There are many different approaches to social justice, such as egalitarianism, utilitarianism, and libertarianism,[23] to name a few. Decisions about whether to fund research that entails some risk should consider how the risks and benefits associated with conducting that research will be distributed, with an effort to distribute risks and benefits as fairly as possible. When considering pandemic potential, fair distribution of risks and benefits must be considered on a global scale.

Respect for persons: allowing competent individuals to make informed choices, and ensuring that the representatives of individuals lacking capacity to choose can make choices in keeping with the wishes, values, or interests of those represented. Autonomy generally requires informing human research participants, laboratory workers, and the public about the risks of research and eliciting their free and uncoerced decision about whether to subject themselves to those risks. In the case of the public, mechanisms for representative decision-making and publicly accountable governance may be needed, as getting consent directly from the members of the public may be impracticable.

[22] *New Directions. The Ethics of Synthetic Biology and Emerging Technologies*. Presidential Commission for the Study of Bioethical Issues, December 2010. http://bioethics.gov/sites/default/files/PCSBI-Synthetic-Biology-Report-12.16.10_0.pdf
[23] Nozick, R., *Anarchy, State, and Utopia*. New York: Basic Books, 1974.

Scientific freedom: avoiding unnecessary interference with scientific research, debate, or publication. Scientific freedom includes an entitlement to avoid interference unless necessary (negative freedom), but not the affirmative right to receive funding or other forms of support for a particular project (positive freedom). Scientific freedom implies a duty of compliance with norms and regulation to promote the responsible conduct of research and protect participants in research and the public. As a corollary to the principle of scientific or intellectual freedom, the Bioethics Commission endorses a principle of regulatory parsimony, requiring "only as much oversight as is truly necessary to ensure justice, fairness, security, and safety while pursuing the public good."[24]

Responsible stewardship: acting in a way that shows concern for children, future generations, and the environment. The Bioethics Commission emphasizes that this is both a domestic and global responsibility that requires "prudent vigilance, establishing processes for assessing likely benefits along with assessing safety and security risks both before and after projects are undertaken."[25]

Procedural Values

The following values apply to the process of decision-making about GOF research and are important to consider when establishing mechanisms to review and/or approve the funding of research proposals involving GOF studies that may entail significant risks.

Public participation & democratic deliberation: making decisions with participation from the public, utilizing respectful debate and inclusive deliberation. Life sciences research is largely a publicly-supported endeavor; therefore, those who allocate funds and conduct life sciences research have a responsibility to be good stewards of public funds and to respond to the interests and concerns of the public. Many, if not all, members of society have a stake in the research enterprise and will be affected directly or indirectly by the benefits and risks stemming from such research. This stakeholder community has diverse values and tolerances for risk, which are important to consider when making decisions about funding and overseeing life sciences research. Some forms of public participation include: oversight by the legislative or executive branches of government, public membership and input on government science advisory committees, other mechanisms of public governance, surveys of public opinion on science policy issues, research models such as community-based participatory research, and efforts by scientists and government officials to share information with the public and better understand the public's interests and concerns. The Bioethics Commission urges the importance of democratic deliberation, as "[a]n inclusive process of deliberation, informed by relevant facts and sensitive to ethical concerns, promotes an atmosphere for debate and decision making that looks for common ground wherever possible and seeks to cultivate mutual respect where irreconcilable differences remain."[26]

[24] *New Directions. The Ethics of Synthetic Biology and Emerging Technologies*. Presidential Commission for the Study of Bioethical Issues, December 2010. http://bioethics.gov/sites/default/files/PCSBI-Synthetic-Biology-Report-12.16.10_0.pdf, p5.
[25] Ibid., p5.
[26] Ibid., p5.

Accountability: taking responsibility for one's actions and being prepared to justify or explain them to others. It is important that decisions to fund research are justifiable to the public and others. Decisions should be justified in terms of substantive and procedural values.

Transparency: sharing with the public the information and assumptions used to make decisions, including uncertainties, controversies, and limitations of analyses. Transparency is an important part of accountability and public participation. It also allows review and reconsideration of policy over time as new facts emerge and analysis evolves.

4.3. Decision-Making Strategies and Frameworks for Evaluating and Managing Risks and Developing Policy

The NSABB identified a number of approaches or frameworks that may be used to guide the making of complex decisions with ethical implications, particularly in the face of uncertainty. These may also be used in developing policies for managing GOF research. Different strategies reflect different attitudes toward risk-taking and some may be more appropriate in some situations than others. The NSABB examined a number of such strategies as it attempted to determine the best option(s) with respect to GOF research that has raised concerns. These options are not mutually exclusive, and elements from more than one may be used together to develop a path forward. The following are decision-making frameworks that were considered.

Maximax: choosing the option with the best possible outcome. Maximax is a relatively simple strategy that focuses on choosing the option with the best possible outcomes. While maximax may be appropriate for making some types of personal choices (e.g. playing games with nothing of value to lose), it may not be appropriate for making science and technology policy decisions because most people would want to take appropriate steps to prevent or mitigate risks regardless of benefits. For GOF studies, use of maximax would involve identifying research with the best possible benefits, regardless of risks.

Maximin: choosing the option with best outcome among the worst possible outcomes. Maximin is a risk-averse approach because it aims to avoid the worst possible outcomes. Maximin is another relatively simple approach, but may present difficulties when applied to making science and technology policy decisions, because it would recommend not developing a new technology if this decision could lead to the worst possible outcome. Since all technologies (and scientific ideas) can conceivably lead to good and bad outcomes, strict adherence to maximin would result in a very cautious approach to science and technology development. For GOF studies, use of maximin would involve identifying studies with risks, and choosing the least risky regardless of benefits.

Expected Utility Theory: choosing the option that maximizes expected utility, where expected utility for a possible outcome = probability x utility. Expected utility theory involves a quantitative balancing of risks and benefits and is inherently a more complex process. Cost-benefit analysis in economics is a form of expected utility theory. A problem with expected utility theory is that sufficient evidence may not always be available to confidently estimate the probabilities involved in

the utility calculus. When this is the case, other approaches may be appropriate. For GOF studies, use of expected utility theory would require quantitatively determining the likelihood of risks and benefits and calculating the resulting utility.

Precautionary approach: involves taking reasonable measures to prevent, minimize, or mitigate risks that are significant and plausible. A measure is "reasonable" if it: 1) appropriately balances the values at stake in the risk management; 2) is proportional to nature of the risk (i.e. greater risks require stronger measures); and 3) is likely to be effective. A risk is "plausible" if there is some scientific evidence that it could occur even if the probability of the risk cannot be confidently estimated. There are many versions of the precautionary principle, including ones that are more or less risk-averse.[27, 28] A precautionary approach, in general, would limit an activity unless the environment, health, or security, are clearly protected. This approach can recognize a potential problem early and prevent harm from occurring but may lead to regulatory burdens or unnecessarily limit activities. This approach might restrict potential GOF research unless the studies are demonstrated to be safe.

Permissive approach: in general, this would allow an activity unless the environment, health, or security, are clearly compromised. This approach may reduce unnecessary regulatory burdens but can result in after-the-fact reaction to harms. This approach might allow certain GOF studies to proceed until they are demonstrated to entail significant risk.

Planned adaptation or risk-based approach: provides a systematic way to deal with managing risks in the face of uncertainty. It involves: 1) preparation to identify the risks and regulatory gaps, including input from a broad range of perspectives; 2) putting measures in place to control risk based on the best information available at the time; 3) systematically gathering data and observing the effects of policies; and 4) updating and revising policies as needed. An example of an adaptive approach is the life cycle approach taken by the Food and Drug Administration when making decisions about whether to approve drugs, when that includes post-market surveillance.[29] For GOF studies, this approach might entail allowing studies that raise concerns to proceed under defined conditions, then evaluating the risk-benefit landscape periodically to determine whether the studies that are permitted should continue, be expanded, or be restricted.

Threshold approach: identifying a risk threshold beyond which, certain studies are given special attention or subject to additional scrutiny or oversight and might preclude certain studies. Implementation would involve defining or describing the studies that would require additional oversight as well as a description of what that oversight would entail. This approach would allow for the identification of studies of concern but might need to be reevaluated if the risk landscape changes and the threshold that was identified is no longer appropriate. For GOF studies, this would

[27] Resnik, D.B., *Environmental Health Ethics*. New York: Oxford University Press, 2013.
[28] Munthe, C., *The Price of Precaution and the Ethics of Risks*. Dordrecht: Springer, 2011.
[29] FDA determinations about whether a new drug is safe and effective are complex, address uncertainty, and involve ongoing monitoring to assess risks and benefits and take appropriate post-marketing actions as necessary. See: *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making*, 2013.
http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf

entail identifying the characteristics of studies involving significant risks that may not be adequately managed and then stipulating further oversight or determining that they should not be conducted.

Point-source approach: involves controlling where certain studies are conducted and under what conditions. This approach would centralize certain research activities, restricting them to designated locations or facilities. For GOF studies that raise concerns this might involve requiring that certain studies only be conducted in facilities with certain biocontainment conditions, biosafety practices, and security measures.

The NSABB used ideas from a number of frameworks to inform its findings and deliberations (Sections 5 and 6). The criteria for identifying GOF research of concern (GOFROC) (see Recommendation 1) reflect a threshold approach. The principles for guiding funding decisions for GOFROC include elements from several of the decision frameworks described above. For instance, an explicit call for a risk-benefit analysis (Recommendation 1, Guiding Principle 3) reflects expected utility theory; however, a strictly quantitative calculation is probably not possible. The principles to guide funding decisions that call for risk mitigation and a restriction to laboratories with a demonstrated capacity to safely carry out the studies (Recommendation 1, Guiding Principles 4, 5 and 7) incorporate elements of point-source and precautionary approaches. An adaptive approach was considered particularly attractive and appropriate for policies aimed at providing oversight of GOF research (Recommendation 3).

4.4. Examination of the Current Policy Landscape

Many U.S. government agencies fund life sciences research in furtherance of their specific missions. In general, research supported by the USG is founded on the principle of scientific merit and goals of the funding agency. Multiple complementary layers of oversight are in place to manage laboratory and other risks associated with federally-funded life sciences research. These policies are intended to provide oversight at various points throughout the research life cycle, from research conception to its publication and translation into practice. These policies include a foundation of occupational health and medicine (for laboratory and clinical workers), laboratory biosafety practices, and policies that address biosecurity risks. Below is a description of the oversight policies in place for federally-funded life sciences research involving pathogens, with discussion of whether and how such policies apply to GOF studies. This analysis is illustrated in Figures 2 and 3 and summarized in Appendix B.

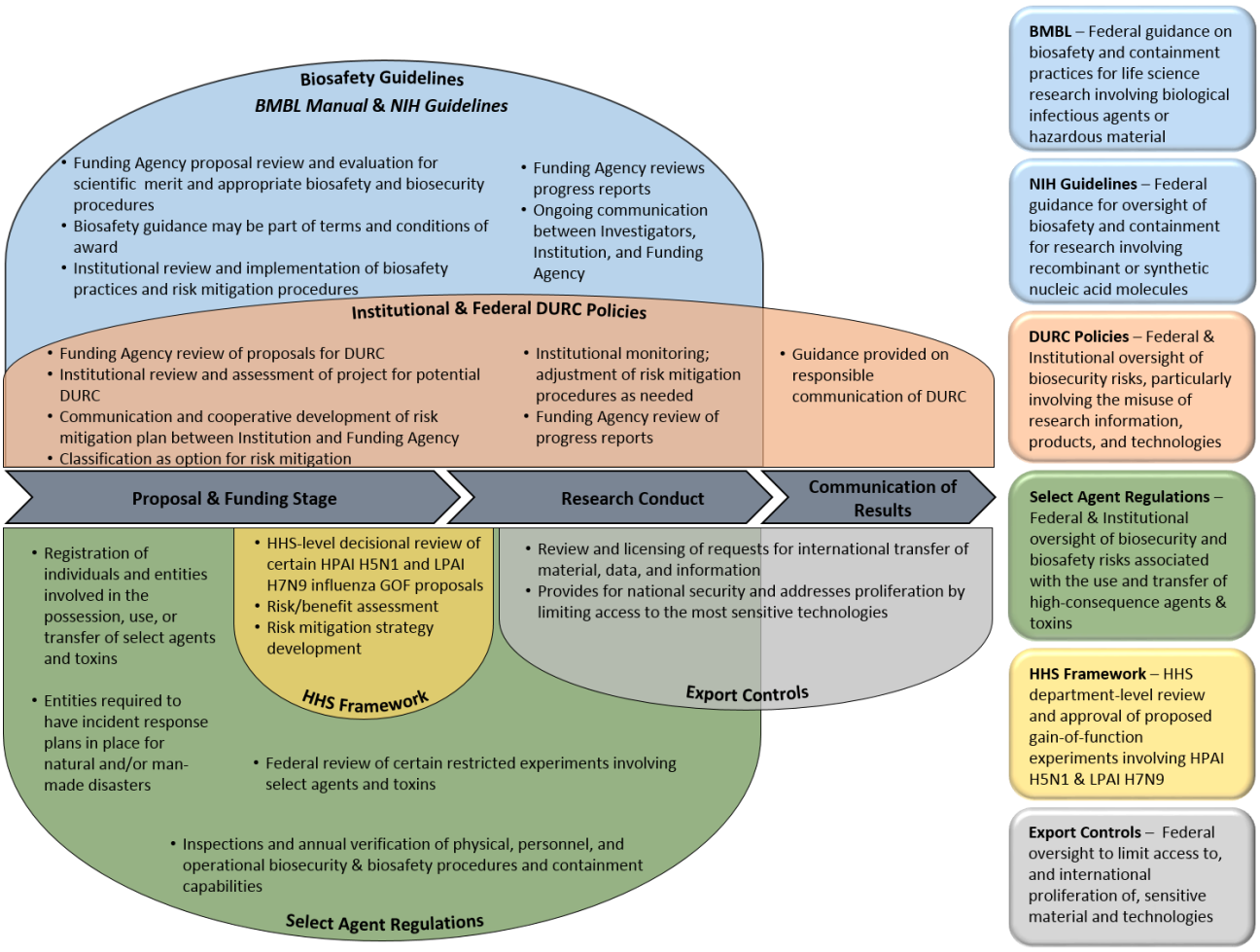

Figure 2. U.S. government oversight of life sciences research involving pathogens. Oversight policies apply at different stages and occur at different levels throughout the research life cycle. See text and Appendix B for descriptions of each policy. These policies have different applicability and scopes and therefore do not apply to all life sciences (or GOF) research projects.

Scientific Merit Review

Departments and agencies within the U.S. government fund diverse portfolios of life sciences research. Funding decisions are based on the scientific merit of a given proposal and the ability of a project to advance the agency's strategic mission. The USG funds life sciences research through a variety of mechanisms including grants, contracts, and cooperative agreements. Each funding agency has its own processes for evaluating research proposals and awarding funds but, in general, proposals are subject to rigorous scientific review by Federal agency staff and often, scientific peers. NIH grant proposals, for example, undergo two levels of review. The first evaluation is by a panel of scientific peer reviewers who score proposals based on scientific merit and other criteria. The second round of review includes discussion of meritorious proposals at public meetings of advisory councils, specific to individual funding institutes and centers within NIH, to determine how proposals fit within their broader strategic objectives.

Biosafety Oversight

Oversight of pathogen research focuses first on ensuring the safe handling of biological agents through appropriate biosafety practices and containment measures, which are addressed by the *Biosafety in Microbiological and Biomedical Laboratories* (*BMBL*)[30], the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*)[31], and other documents. The BMBL and the *NIH Guidelines* provide for federal and institutional biosafety oversight and guidance involving biosafety practices and containment features that are based on risk assessments for specific projects. Such determinations are typically made at the institutional level and are guided by federal guidelines and policies, which are updated as necessary to provide additional guidance for research involving emerging pathogens or technologies. Biosafety is achieved by conducting research under appropriate physical and biological containment levels and employing practices that help to ensure a safe working laboratory environment.

The BMBL is a guidance document developed by CDC and NIH that is generally considered the authoritative reference for laboratory biosafety in the United States. The BMBL provides summary statements for many bacterial, fungal, parasitic, rickettsial, viral, and other agents. These statements describe the characteristics of the pathogen, its natural mode of infection, potential occupational hazards with the agent, and recommendations for laboratory safety and containment. It also describes the fundamentals of biological containment, which include descriptions of proper microbiological practices, safety equipment, and facility safeguards that protect laboratory workers, the environment, and the public from exposure to infectious microorganisms that are handled and stored in the laboratory. It describes the process of biological risk assessment, which enables the appropriate selection of microbiological practices, safety equipment, and facility safeguards that can prevent laboratory-associated infections. It also describes occupational health, immunoprophylaxis, and principles for laboratory biosecurity. The BMBL is updated periodically to refine guidance based on new knowledge and experiences and to address contemporary issues that present new risks that confront laboratory workers and public health.

> **Analysis:** The BMBL does not address GOF studies *per se* but does include summary statements and biocontainment guidance for research involving various influenza strains (including contemporary and non-contemporary human, high and low pathogenic avian, swine, the 1918 influenza strain, and reassortant viruses) and SARS-CoV. MERS-CoV had not emerged at the time of the last BMBL update, but interim laboratory biosafety guidance was issued by CDC.[32]

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[30] *Biosafety in Microbiological and Biomedical Laboratories* (BMBL), 5th Edition. http://www.cdc.gov/biosafety/publications/bmbl5/

[31] *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (NIH Guidelines), November 2013. http://osp.od.nih.gov/sites/default/files/NIH_Guidelines.html

[32] *Interim Laboratory Biosafety Guidelines for Handling and Processing Specimens Associated with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) – Version 2*. http://www.cdc.gov/coronavirus/mers/guidelines-lab-biosafety.html [last updated June 18, 2015]

The BMBL is not a regulatory document. U.S. funding agencies may require it be followed as a term and condition of funding but, in general, compliance with the BMBL is voluntary. In addition, the BMBL provides general biosafety guidance but does not describe detailed procedures or experiment-specific containment protocols.

The *NIH Guidelines* specify the practices for safely constructing and handling: recombinant nucleic acid molecules; synthetic nucleic acid molecules, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules; and cells, organisms, and viruses containing such molecules. The *NIH Guidelines* apply to basic and clinical research involving recombinant or synthetic nucleic acid molecules conducted at or sponsored by institutions that receive NIH funding for any such research. Compliance with the *NIH Guidelines* is required by NIH as a term and condition of award of funding. Other USG agencies may also require compliance with the *NIH Guidelines*.

The *NIH Guidelines* focus on the concepts of risk assessment, risk group classification of agents based on their ability to cause disease in humans and the availability of medical countermeasures, physical and biological containment levels, practices, personal protective equipment, and occupational health. To help ensure the safe conduct of this research, the *NIH Guidelines* specify roles and responsibilities of investigators and institutions. Institutions subject to the *NIH Guidelines* must establish Institutional Biosafety Committees (IBCs) composed of members with appropriate expertise, to review and approve such research. IBCs provide local oversight and ensure compliance with the *NIH Guidelines*. Certain higher risk experiments require review by the Recombinant DNA Advisory Committee (RAC)[33] and specific approval by the NIH Director as Major Actions. These experiments involve the deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally, if such acquisition could compromise the ability to control disease agents in humans, veterinary medicine or agriculture.

In order to continue to provide appropriate guidance for emerging pathogens or experimental approaches, the *NIH Guidelines* are updated periodically. The *NIH Guidelines* have been amended to include additional guidance for work with Risk Group 3 influenza viruses (1918 H1N1, H2N2, highly pathogenic avian influenza (HPAI) H5N1), to specify enhancements to biosafety level 3 containment, practices, and to incorporate occupational health requirements. In 2012, the *NIH Guidelines* were amended again to require further enhancements to facilities, biosafety equipment and practices, including occupational health practices, for research involving HPAI H5N1 strains that are transmissible among mammals by respiratory droplets.

Analysis: The *NIH Guidelines* provide guidance on risk assessment and appropriate containment and practices for conducting research involving recombinant or synthetic nucleic acids, which would

[33] The Recombinant DNA Advisory Committee (RAC) is a federal advisory committee that provides recommendations to the NIH Director related to basic and clinical research involving recombinant or synthetic nucleic acid molecules. See: http://osp.od.nih.gov/office-biotechnology-activities/biomedical-technology-assessment/hgt/rac

apply to most government-funded GOF research. Some IBCs also review and approve non-recombinant pathogen research, however, not all institutions require their IBCs to do so. While the *NIH Guidelines* are often used as a model of biosafety guidance by the broader scientific community, compliance is required only by institutions receiving funding from the NIH for research involving recombinant or synthetic nucleic acid molecules. Therefore, some GOF studies may not be subject to the *NIH Guidelines* depending on whether the institution where the research is being conducted is subject to the *NIH Guidelines*.

The Federal Select Agent Program

The *Public Health Security and Bioterrorism Preparedness and Response Act of 2002*[34] requires the U.S. Departments of Health and Human Services (HHS) and Agriculture (USDA) to establish and regulate a list of select agents — biological agents and toxins that have the potential to pose a severe threat to public health and safety or animal or plant health or animal or plant products. The Federal Select Agent Program (FSAP) is administered jointly by the HHS Centers for Disease Control and Prevention and USDA Animal and Plant Inspection Service. The FSAP oversees the possession, use and transfer of biological select agents and toxins. The Select Agents and Toxins List is reviewed and updated biennially. Under the select agents regulations, individuals and institutions that possess, use, or transfer any select agent are required to be registered, follow appropriate biosafety procedures, and undergo periodic inspections. Individuals must be registered with the FSAP to have access to select agents or toxins, which requires that they undergo a security risk assessment performed by the Federal Bureau of Investigation (FBI). There are legal penalties for failing to comply with the select agent regulations.

In addition to the agents and toxins on the list, the select agent regulations apply to some genetic elements, including nucleic acids that are immediate precursors to infectious forms of any select agent viruses (i.e., complete positive strand RNA viral genomes), as well as some nucleic acids that encode select toxins. Select agent regulations also apply to genetically-modified select agents and toxins. Restricted experiments are described in the regulations and involve the deliberate transfer of or selection for a drug resistance trait to select agents that are not known to acquire the trait naturally. If the acquisition of resistance is to a first-line drug that could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture, the restricted experiment requires special review and approval by the SAP. Some attenuated strains of select agents may be excluded from the regulations based upon a determination that the attenuated strain or modified toxin does not pose a severe threat to public, plant, or animal health or safety. The list of select agents and toxins is reviewed and updated biannually. The Intragovernmental Select Agent and Toxin Technical Advisory Committee serves as an advisory group to the FSAP and provides recommendations on the addition or deletion of agents or toxins to/from the select agent list. Following the disclosure of laboratory incidents at Federal

[34] *Public Health Security and Bioterrorism Preparedness and Response Act of 2002*. https://www.gpo.gov/fdsys/pkg/STATUTE-116/pdf/STATUTE-116-Pg594.pdf

facilities involving select agents in 2014, two advisory committees issued recommendations on ways to strengthen the FSAP.[35, 36] Plans to implement these recommendations are also in place.[37]

Analysis: GOF studies are subject to oversight by the FSAP if they involve pathogens on the select agent list. Researchers and institutions performing such studies must receive favorable security risk assessments by the FBI, register with the FSAP, receive training on the proper procedures and practices for handling such agents, and abide by other aspects of the regulations. SARS-CoV, HPAI H5N1 influenza, and 1918 influenza viruses are select agents. Restricted experiments that would entail conferring antiviral resistance to these viruses would require additional review and approval prior to being conducted. However, MERS-CoV is not a select agent. GOF experiments involving MERS, and other agents not included on the select agent list, would not be subject to oversight by the FSAP (though they could be subject to other federal and institutional biosafety oversight). The FSAP is underpinned by a regulatory requirement that applies to non-USG funded (i.e., private sector funded) pathogen research as well.

Federal and Institutional Oversight of Life Science Dual Use Research of Concern

The U.S. government has issued policies for the oversight of life sciences DURC. These policies focus oversight on research involving 15 high-consequence pathogens and toxins[38] that involve seven categories of experimental activity, which are projects that can be reasonably anticipated to:

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 above.

[35] *Report of the Federal Experts Security Advisory Panel*. U.S. Government, December 2014.
[36] *Fast Track Action Committee Report: Recommendations on the Select Agent Regulations Based on Broad Stakeholder Engagement*, U.S. Government, October 2015.
[37] Lisa Monaco and John Holdren White House Memorandum, October 29, 2015, Next Steps to Enhance Biosafety and Biosecurity in the United States. https://www.whitehouse.gov/sites/default/files/docs/10-2015_biosafety_and_biosecurity_memo.pdf
[38] Section III of the *United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern* and Section 6.2.1 of the *United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern.* The agents within the scope of the USG DURC policies are the 13 Tier 1 select agents plus HPAI H5N1 and 1918 influenza virus.

Projects involving any of the 15 agents and that could be anticipated to involve any of these seven experimental effects are then determined to be DURC if they then meet the definition of DURC listed in the policy.[39]

The DURC policies outline a coordinated approach to oversight involving the federal funding agencies and institutions that conduct such research. The policy for federal oversight, issued in March 2012, requires Federal Departments and Agencies to review proposed and ongoing research projects to identify any that constitute DURC.[40] The policy for institutional oversight, issued in September 2014, articulates responsibilities of research institutions in identifying and managing DURC. Research institutions are to establish an Institutional Review Entity (IRE) to review research subject to the policy to determine whether any such research involves any of the seven experimental effects, and if so, whether the research constitutes DURC. IREs may review projects not specifically covered under the DURC policies but such additional reviews are voluntary.

When DURC is identified—either by a funding agency or a research institution—the funder and institution are to work collaboratively to develop a risk mitigation plan to help ensure that the research is conducted and communicated in a responsible manner. DURC risk mitigation plans are approved by the federal funding agency and are reviewed on an annual basis by the funder and the institution. Specific risk mitigation measures may be incorporated into a term of award. Risk mitigation may involve modifying the design or conduct of the research in order to address the same scientific question in a manner that poses fewer biosafety or biosecurity risks. Other measures may involve applying enhanced biosafety or biosecurity measures, evaluating the effectiveness of extant medical countermeasures prior to proceeding with particular studies, or establishing a more frequent schedule of DURC reviews to more closely monitor the research as it evolves. It is also expected that a communication plan will be established to ensure that DURC is communicated in a responsible manner. Federal funding agencies can provide advice and guidance on responsible communication, but recommendations on how to communicate research typically are not binding; ultimately, investigators and journal editors decide on how to communicate the research.

> **Analysis:** Some of the seven experimental effects within the scope of the DURC policies could be considered GOF studies. However, GOF studies that involve these effects are only subject to DURC oversight if they involve one of the 15 agents listed in the policies. Only two influenza viruses are within the scope of these policies; SARS and MERS coronaviruses are not. The DURC policies are also inherently subjective. While the list-based approach clearly delineates projects that are subject

[39] The definition of dual use research of concern listed in the *USG Policy for Oversight of Life Science DURC* (USG, March 2012) and the *USG Policy for Institutional Oversight of Life Sciences DURC* (USG, September 2014) is "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."

[40] The policy for Federal DURC oversight requires Federal funding agencies to compile biannual inventories of projects identified as being subject to DURC oversight. As part of this process, Federal agencies have been identifying projects involving MERS and LPAI H7N9 influenza and proactively managing risks associated with those projects, as necessary.

to oversight, the definition of DURC, and to a lesser extent, the seven experimental effects, all require significant judgment and interpretation.

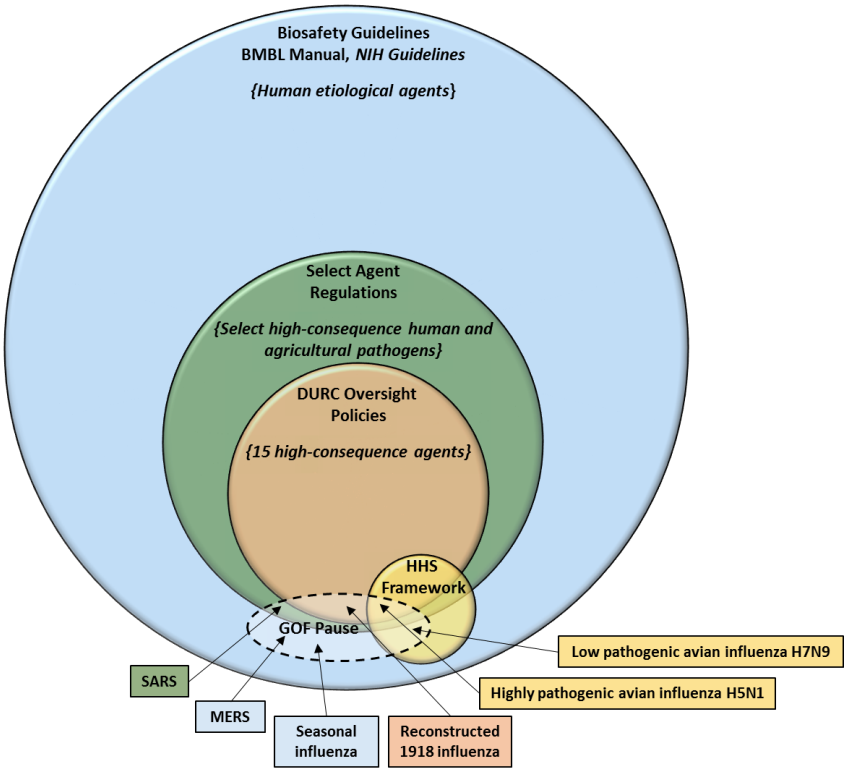

Figure 3. Comparison of the scope of different policies for the oversight of life sciences research involving pathogens. Oversight policies apply to research involving specified agents or procedures. GOF studies involving pathogens or manipulations covered under a given policy would be subject to oversight described by that policy.

Federal-Level Review of Certain Gain-of-Function Studies

The only U.S. policy that specifically addresses GOF studies is the *Framework for Guiding U.S. Department of Health and Human Services Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets (HHS Framework)*, issued by HHS in February, 2013. Under the *HHS Framework*[41, 42] certain proposals with the potential for generating highly pathogenic avian influenza H5N1 viruses that are transmissible among mammals by respiratory droplets receive special review and

[41] *A Framework for Guiding U.S. Department of Health and Human Services Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets*. U.S. Department of Health and Human Services, February 2013. http://www.phe.gov/s3/dualuse/Documents/funding-hpai-h5n1.pdf

[42] Patterson, A., et al. *A Framework for Decisions about Research with HPAI H5N1 Viruses*. Science. 2013 Mar 1: 339(6123): 1036-1037.

approval before being funded by HHS. This policy was subsequently expanded to include review of similar proposals involving low pathogenic avian influenza H7N9 viruses.[43]

Funding agencies within HHS (including NIH, CDC, and FDA) review relevant proposals for risks and benefits, and refer relevant studies to a Department-level review group, the HHS HPAI H5N1 Gain-of-Function Review Group, for advice prior to funding the proposal. The review group includes a wide range of interdisciplinary expertise from across HHS, and can draw on additional experts within the U.S. government if necessary. HHS reviews GOF research proposals that are subject to the *HHS Framework* and makes recommendations to HHS funding agencies about whether the study is acceptable for funding and whether additional measures may be needed to mitigate risks. HHS considers a number of factors including the following criteria, which must be met in order for a GOF study to be acceptable to receive HHS funding:

1. The virus anticipated to be generated could be produced through a natural evolutionary process;
2. The research addresses a scientific question with high significance to public health;
3. There are no feasible alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach;
4. Biosafety risks to laboratory workers and the public can be sufficiently mitigated and managed;
5. Biosecurity risks can be sufficiently mitigated and managed;
6. The research information is anticipated to be broadly shared in order to realize its potential benefits to global health; and
7. The research will be supported through funding mechanisms that facilitate appropriate oversight of the conduct and communication of the research

Analysis: The *HHS Framework* requires an explicit consideration of the risks and benefits associated with certain GOF studies prior to making a funding decision. This allows HHS to identify potential risks prior to funding the research and make recommendations about risk mitigation—including consideration of alternative approaches or modifying the experimental design—at the outset. This review process also involves broader expertise including, ethical, legal, security, intelligence, and others. The criteria that must be met in order to receive funding are subject to judgment and interpretation. The scope of the *HHS Framework* is also quite narrow and currently covers only projects involving two influenza viruses and that involve one specific experimental outcome (mammalian transmission by respiratory droplets); other GOF studies involving different pathogens do not receive this pre-funding review.

Reviews under this framework are conducted by a group internal to the U.S. government. Reviewing GOF studies in a confidential setting allows for the examination of potentially sensitive scientific, proprietary, and personal information, and allows for discussions that may be sensitive from a national security or public health preparedness perspective. However, such reviews do not achieve the level of transparency desired by some stakeholders and also make it difficult to independently assess the effectiveness of the review process. Finally, the *HHS Framework* was in

[43] Jaffe, H.W., et al. *Extra Oversight for H7N9 Experiments*. Science. 2013 August 16: 341(6147):713-714.

place for less than two years when the October 2014 funding pause was enacted and only a handful of GOF projects have been reviewed to date, making it difficult to fully evaluate this policy's strengths and limitations.

In response to the funding pause[44], the National Institute for Allergy and Infectious Diseases (NIAID), within the NIH, developed a process for considering on a case-by-case basis studies that might be subject to the GOF pause. Reviews by NIAID include a detailed consideration of the science, including a specific examination of the viral strains in question and specific experiments being proposed. NIAID begins by consulting the investigators and an internal NIAID group determines whether the projects are subject to the pause. When identifying projects subject to the funding pause, NIAID used a fairly broad interpretation of the language set forth in the pause statement and paused, at least initially, more projects than were ultimately determined to meet the scope of the pause policy. NIAID also sought exceptions (using a mechanism provided for in the USG's moratorium statement) for projects that were deemed critical to public health or national security. In determining whether an exception to the pause might be warranted, NIAID considered the intent of the research, the availability of countermeasures, potential alternative approaches, the risks of not conducting the research, and the available mechanisms for ongoing oversight. Exceptions may only be granted by the NIH Director.

Analysis: NIAID's process for identifying GOF projects that are subject to the funding pause is rigorous and serves as an example of federal-level identification and review of GOF studies of potential concern. It includes extensive scientific review and is performed by individuals with experience reviewing projects for DURC potential. It does not involve the same expertise that is provided under *HHS Framework* reviews such as national security, ethics, or legal. Given the limited number of projects that have been examined by NIAID it is difficult to fully evaluate the effectiveness of this approach.

Sharing and Communicating Scientific Findings and Research Products

The majority of life sciences research is conducted in academic settings and the results are communicated openly in scientific journals and public forums. For a small subset of research with national security implications, there are policies in place to restrict access to scientific information or products. Under National Security Decision Directive (NSDD) 189, dissemination of fundamental research is to remain unrestricted to the maximum extent possible and in instances where restriction is necessary for national security, classification is to be the appropriate mechanism for restricting access.[45] Life sciences research that requires classification is classified at its outset and conducted in

[44] *United States Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses*. U.S. Government, October 17, 2014. http://www.phe.gov/s3/dualuse/documents/gain-of-function.pdf

[45] NSDD 189 (September 21, 1985) defines fundamental research as "basic and applied research in science and engineering, the results of which ordinarily are published and shared broadly within the scientific community, as distinguished from proprietary research and from industrial development, design, production, and product utilization, the results of which ordinarily are restricted for proprietary or national security reasons." https://research.archives.gov/id/6879779

designated facilities that are equipped with the infrastructure and personnel with appropriate level national security clearances to perform the research. Retroactively classifying research that was conducted in an unclassified setting is immensely challenging and may be unfeasible.

Export controls are federal regulations that regulate exports that have national security or foreign policy implications. Certain materials and information related to biological agents and genetic elements, vaccines, equipment, and related technologies are covered by export control regulations. Furthermore, the transfer of controlled information to a foreign national within the United States may be considered to be an export to that foreign national's country. The regulations are complex but, in general, they specify which items, when being shipped to which destinations, will require an export license. Life sciences research that is openly published is not subject to export controls, but information that is withheld from publication by the investigator or research institution based on security concerns may become subject to export control regulations, and an export license may be required before that information can be shared with foreign nationals. Most biological research activities that are subject to export controls fall under the Department of Commerce's Export Administration Regulations, which control items that have both military and civilian applications.[46] However, some might fall under the jurisdiction of the State Department's International Traffic in Arms Regulations.[47]

A number of scientific journals and families of journals have policies for identifying and reviewing manuscripts that raise biosecurity and biosafety concerns. These efforts are commendable but some have noted the challenges associated with trying to identify DURC or implement risk mitigation measures at the publication stage.[48, 49] NSABB has previously developed strategies and a risk assessment tool to assist in the development of a responsible communication plan for DURC, which might include altering the content, distribution, or timing of a publication.[50] The U.S. government has no authority to mandate redaction, restriction, or classification of a scientific publication that it does not own or control, and efforts to develop a mechanism for restricting communication of unclassified information to only those who require access, remain challenging and to date, unsuccessful.[51]

> **Analysis:** Once a study has been completed, it is difficult to limit the distribution of or access to the findings, particularly if the study was conducted in an open, academic environment. Oversight of DURC, and in particular GOF studies involving pathogens with pandemic potential, may be most

[46] Export Administration Regulations, 15 CFR Parts 730, 734, 736, 742, 744, and 745. https://www.bis.doc.gov/index.php/regulations/export-administration-regulations-ear

[47] International Traffic and Arms Regulations, 22 U.S.C. 2778 https://www.pmddtc.state.gov/regulations_laws/itar.html

[48] Casadevall, A., et al. *Dual-Use Research of Concern Review at American Society for Microbiology Journals*. mBio 6(4):e01236-15. 2015.

[49] Atlas, R., et al. Journal editors and authors group statement on scientific publication and security. Science, 299:1149. 2003.

[50] *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information*. National Science Advisory Board for Biosecurity, June 2007. http://osp.od.nih.gov/sites/default/files/resources/Framework%20for%20transmittal%20duplex%209-10-07.pdf

[51] Research information produced under a U.S. government grant is not considered to be owned or controlled by the Federal Government. However, under the Invention Secrecy Act, the U.S. government can nevertheless impose secrecy orders on patent applications if the publication or disclosure of the ensuing patent would be detrimental to national security.

feasible and effective if it occurs 1) upstream (i.e., during the review of proposed studies and before experiments are initiated) and 2) in an ongoing manner while the research is being conducted. Classification may be an option for certain GOF studies, but this would require these studies to be conducted in significantly different settings than they are currently. Further, although certain GOF studies have raised concerns about whether they should be published, it is unlikely that such manuscripts would meet the criteria for classification under U.S. government classification authorities. It is conceivable that certain studies should not be undertaken at all or not published because of unanticipated findings. However, it may be very difficult to predict at the proposal stage whether findings of concern might arise during the experiment, and unanticipated findings that raise concern may be unavoidable. Individual investigators or journal editors have, on security grounds, decided to redact certain material from publication, possibly triggering export controls on the redacted material, but in general such a redaction could not be mandated by the U.S. government.

Broader U.S. Biosafety and Biosecurity Efforts

Parallel to the GOF deliberative process, the USG also initiated broader reviews of biosafety and biosecurity policies and procedures following a series of laboratory incidents occurring at federal institutions in 2014. The Holdren-Monoco memorandum[52] called for federal and non-federal reviews to provide recommendations to strengthen the biosafety and biosecurity practices and oversight system for USG funded research. The memo outlined three immediate actions for U.S. government Departments and Agencies:

1. Conduct a comprehensive review of current biosafety and biosecurity protocols to ensure adequacy and appropriateness for today's infectious disease research
2. Inventory and document culture collections
3. Increase attentiveness throughout research community to ensure the safety of laboratory workers and the American public.

In September 2015, The White House National Security Council tasked the Federal Experts Security Advisory Panel (FESAP) to 1) identify needs and gaps and make recommendations to optimize biosafety, biosecurity, oversight, and inventory management and control for biological select agents and toxins (BSAT); 2) identify actions and any regulatory changes to improve biosafety and biosecurity; and 3) identify an approach to determine the appropriate number of high-containment U.S. laboratories required to possess, use, or transfer BSAT. To obtain broad stakeholder recommendations, the National Science and Technology Council established the Fast Track Action Committee on Select Agent Regulations (FTAC-SAR). In October 2015, USG released the FESAP and FTAC-SAR recommendations[53] that address: the culture of responsibility, oversight, outreach and education; applied biosafety

[52] August 2014 White House Memorandum – Enhancing Biosafety and Biosecurity in the United States https://www.whitehouse.gov/sites/default/files/microsites/ostp/enhancing_biosafety_and_biosecurity_19aug2014_final.pdf

[53] *Report of the Federal Experts Security Advisory panel.* December 2014. http://www.phe.gov/s3/Documents/fesap.pdf; *Fast Track Action Committee Report: Recommendations on the Select Agent Regulations Based on Broad Stakeholder Engagement.* http://www.phe.gov/s3/Documents/ftac-sar.pdf

research; incident reporting; material accountability; inspection processes; and regulatory changes and guidance to improve biosafety and biosecurity. The USG is implementing these recommendations.[54]

[54] *Implementation of Recommendations of the Federal Experts Security Advisory Panel and the Fast Track Action Committee on Select Agent Regulations*, October 2015. http://www.phe.gov/s3/Documents/fesap-ftac-ip.pdf

5. Findings of the NSABB

In developing its findings (Box 2), the NSABB considered the results of the RBA, policy analysis and decision-making frameworks, discussions of ethics, and perspectives of domestic and international stakeholders.

Box 2. Summary of Findings

Finding 1. There are many types of GOF studies and not all of them have the same level of risks. Only a small subset of GOF research—GOF research of concern (GOFROC)—entail risks that are potentially significant enough to warrant additional oversight.

Finding 2. The U.S. government has several policies in place for identifying and managing risks associated with life sciences research. There are several points throughout the research life cycle where, if the policies are implemented effectively, risks can be managed and oversight of GOF research of concern could be implemented.

Finding 3. Oversight policies vary in scope and applicability, and do not cover all potential GOFROC, therefore, current oversight is not sufficient for all GOF research of concern.

Finding 4. An adaptive policy approach is a desirable way to ensure that oversight and risk mitigation measures remain commensurate with the risks associated with the research and that the benefits of the research are being fully realized.

Finding 5. There are life sciences research studies, including possibly some GOF research of concern, that should not be conducted because the potential risks associated with the study are not justified by the potential benefits. Decisions about whether specific GOFROC should be permitted will entail an assessment of the potential risks and anticipated benefits associated with the individual experiment in question. The scientific merit of a study is a central consideration during the review of proposed studies but other considerations, including legal, ethical, public health, and societal values are also important and need to be taken into account.

Finding 6. Managing risks associated with GOF research of concern, like all life sciences research, requires both federal and institutional oversight, awareness and compliance, and a commitment by all stakeholders to safety and security.

Finding 7. Funding and conducting GOF research of concern encompasses many issues that are international in nature.

Finding 1. There are many types of GOF studies and not all of them have the same level of risks. Only a small subset of GOF research—GOF research of concern (GOFROC)—entail risks that are potentially significant enough to warrant additional oversight. As with all life sciences research involving pathogens, GOF studies entail inherent biosafety and biosecurity risks. GOF research involving the generation of pathogens with pandemic potential involves the greatest risks. A laboratory accident involving such a pathogen could potentially release a pathogen that could spread rapidly and efficiently through the human population. A laboratory pathogen with enhanced characteristics could also, if malevolently used, pose a greater threat to national security or public health than similar misuse involving a wild type pathogen. The probability that such events would occur is low but non-zero and the potential consequences are uncertain but potentially significant.

Gryphon's biosafety risk assessment identified studies involving enhanced transmissibility, enhanced pathogenicity, and evasion of immunity as entailing the highest risks for coronaviruses, seasonal influenza, and avian influenza.[55] Manipulations that increase transmissibility, increase pathogenicity, and enable a pathogen to more readily spread through the population have the greatest potential to increase risk; in some strains even a moderate increase might be a concern.

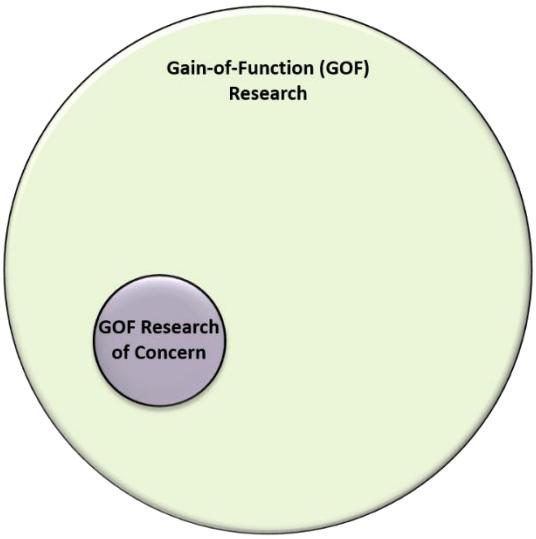

Figure 4. Conceptual categorization of GOF research involving human pathogens. GOF research includes a broad range of experimental approaches, most of which do not raise significant concerns. GOF research of concern represents a small subset of all GOF research that can be reasonably anticipated to result in generation of a pathogen with pandemic potential, described as a pathogen that is likely both highly transmissible and highly virulent in humans.

To help categorize studies based on the level of concern stemming from their associated risks, the NSABB has designated studies as: GOF research and GOF research of concern (GOFROC) (Figure 4). The term "GOF research" would encompass all studies whereby some characteristic of the pathogen is enhanced by experimental manipulation. The vast majority of GOF research does not raise any significant concerns; these studies do not entail novel or significant risks and are subject to appropriate oversight to manage risks. GOF research of concern, or GOFROC, represents the small subset of studies that result in the generation of a pathogen with pandemic potential—that is, a pathogen that is highly virulent and highly transmissible, as judged by its likely ability to spread among human populations (see Recommendation 1 for more thorough descriptions of these attributes).

[55] *Risk and Benefit Analysis of Gain-of-Function Research, Final Report*. Gryphon Scientific, April 2016. http://www.gryphonscientific.com/wp-content/uploads/2016/04/Risk-and-Benefit-Analysis-of-Gain-of-Function-Research-Final-Report.pdf

Finding 2. The U.S. government has several policies in place for identifying and managing risks associated with life sciences research. There are several points throughout the research life cycle where, if the policies are implemented effectively, risks can be managed and oversight of GOF research of concern could be implemented. Federally-funded life sciences research in the U.S. is conducted in accordance with occupational health and safety laws and regulations, the *NIH Guidelines*, the BMBL, policies for the federal and institutional oversight of DURC, the select agent regulations, export control regulations, international treaties and agreements, and other relevant policies. HHS has also developed a framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses. Together, these policies aim to mitigate biosafety risks, biosecurity risks, and other risks associated with life sciences research, including many of the GOF studies that have raised concerns.

U.S. policies involve oversight and help manage risks during several phases throughout the research life cycle including the proposal review, the funding decision, during the conduct of the research, and at the time the research is being communicated. There are also numerous entities that are responsible for providing oversight, managing risks or issuing guidance, including funding agencies, federal advisory committees, institutional review and compliance committees, individual investigators, and journal editors.

While effective implementation of these policies can manage much of the risk associated with life sciences research, some GOFROC is more thoroughly monitored than others. Additionally, coverage under current policies is incomplete (e.g., GOFROC funded and conducted by/within the private sector may not be subject to federal oversight). Institutional oversight also varies. For example, IBCs differ in capabilities and expertise, and institutional resources and cultures vary. In addition, there is limited data describing the rate and extent of laboratory accidents, near misses, and security breaches. Little comprehensive data about these critical issues exist, and no entity is currently authorized to collect all of the desirable information that would inform risk-benefit assessments.

Finding 3. Oversight policies vary in scope and applicability, and do not cover all potential GOFROC, therefore, current oversight is not sufficient for all GOF research of concern. U.S. policies are applicable to some but not all GOFROC. Risks associated with GOFROC that does not involve select agents or pathogens subject to oversight under the USG DURC policies or the *HHS Framework*, would largely be managed at the institutional level, in accordance with guidance provided in the *NIH Guidelines* and BMBL. In general, GOFROC that is not conducted with USG funds is not subject to oversight by a federal funding agency.[56] Other countries also fund and conduct life sciences research, including GOF studies, which are beyond the purview of the U.S. government as well.

[56] Research involving a select agent, whose oversight is articulated in Federal statute and requires compliance from all researchers and institutions, would be subject to Federal oversight, regardless of the funding source. Some privately-funded research being conducted at institutions that receive Federal funding for that research may also be subject to oversight under the *NIH Guidelines*, USG DURC policies, or other policies.

In addition, the USG oversight policies vary. Different policies are aimed at managing different risks, and each is implemented by various Federal Departments and Agencies. This can result in redundancies as well as gaps in oversight, as the various policies are not sufficiently harmonized.

Finally, full compliance with policies is essential to their effectiveness. The effectiveness of policies can be enhanced by a commitment to proper implementation and enforcement at the federal, institutional, and individual investigator levels. This can include training, education, codes of conduct, and other mechanisms for continuing to build a culture of responsibility.

Finding 4. An adaptive policy approach is a desirable way to ensure that oversight and risk mitigation measures remain commensurate with the risks associated with the research and that the benefits of the research are being fully realized. Many, but not all, of the policies that apply to GOF studies are adaptive in nature. The BMBL is updated periodically. The *NIH Guidelines* and the select agent programs are updated or revised periodically as well and both have processes for seeking external advice for informing policy development. The DURC policies and the *HHS Framework* do not have articulated mechanisms for reviewing or updating the policies, or for seeking input on policy development (though both state an intention to be updated as necessary).

Great uncertainty is inherent in conducting risk-benefit assessments with currently available data and the uncertainty associated with several key parameters of the risk and benefit assessment made its interpretation challenging. Such uncertainty about risks and benefits may also make risk management difficult. An adaptive policy approach would facilitate refinement of GOF risk management as knowledge and experience are acquired.

Finding 5. There are life sciences research studies, including possibly some GOF research of concern, that should not be conducted because the potential risks associated with the study are not justified by the potential benefits. Decisions about whether specific GOFROC should be permitted will entail an assessment of the potential risks and anticipated benefits associated with the individual experiment in question. The scientific merit of a study is a central consideration during the review of proposed studies but other considerations, including legal, ethical, public health, and societal values are also important and need to be taken into account. Examples of studies that should not be conducted for ethical reasons include those that: involve human subjects who have not been provided and signed an informed consent document approved by an IRB; are anticipated to cause undue harm to a human subject; or that entail risks that are unjustifiable in the light of the benefits. For example, the development of biological weapons is unethical and has been banned by international treaty.[57]

[57] Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. Signed at London, Moscow and Washington on 10 April 1972; entered into force on 26 March 1975. Depositaries: UK, US and Soviet governments. http://www.opbw.org/

There may be GOFROC that should not be funded on ethical grounds but it is difficult to identify or describe such studies based on general or hypothetical descriptions. An ethical evaluation of a research study would entail an evaluation of the risks and benefits, which requires a thorough understanding of the scientific details of the proposal, including its aims and any foreseeable adverse consequences. In addition, the scientific, public health, and national security landscape is dynamic. Public health needs change as new diseases emerge. Risks may arise or diminish based on the availability (or lack) of effective countermeasures. Benefits may become more or less likely to be realized based on other enabling factors, such as new scientific findings or technologies. Decisions to fund GOF studies must take into account these nuances in the risk-benefit landscape.

The NSABB did not seek to develop a list of studies that should not be conducted but rather sought to develop general principles that describe what is acceptable and not acceptable for funding. A principle-based approach to guiding funding decisions is adaptable and likely more effective. However, one example of a scientific study that should not be conducted might be the insertion of a virulence gene from an unrelated organism into the genome of a virus that is transmissible through the respiratory route, which would be highly unlikely to occur through natural recombination. This study, and others that involve the transfer of virulence genes between disparate microbes would appear to lack public health benefit, since the novel, laboratory-generated pathogen is unlikely to arise naturally and would therefore entail potentially significant and unnecessary risks.

Finding 6. Managing risks associated with GOF research of concern, like all life sciences research, requires both federal and institutional oversight, awareness and compliance, and a commitment by all stakeholders to safety and security. Biosafety and biosecurity risks associated with life sciences research are managed through engineering controls, laboratory practices, medical surveillance and support, appropriate training, and other interventions. However, GOFROC has the potential to generate strains with significant risks that may require additional oversight and containment mechanisms. Managing the risks associated with GOFROC in particular requires a commitment to safety and security at the federal and institutional level that includes a strong foundation of training and a demonstrated commitment to compliance by the research institution, and the individual investigators at the local level.

Finding 7. Funding and conducting GOF research of concern encompasses many issues that are international in nature. The potential risks and benefits associated with GOFROC are international in nature. Laboratory accidents and intentional misuse could have global consequences. The benefits of vaccine and other medical countermeasure development and disease surveillance also have important international implications. The research enterprise is international as well, and GOFROC is being conducted in a number of countries already. While USG funding policy regarding GOFROC only directly affects domestic and international research within the purview of the U.S. government, decisions made by the United States in this area can influence GOFROC oversight policies globally.

Notably, as highlighted during presentations at NSABB and National Academies meetings, GOF research and GOFROC are being conducted in a number of countries and a variety of oversight mechanisms at the national and regional level are in place. In addition, a number of countries and international scientific organizations have been considering issues related to biosafety, biosecurity, dual use research, and GOFROC.[58, 59, 60, 61, 62, 63] International perspectives are important to the development of U.S. policy in this area and global engagement is necessary to foster effective oversight mechanisms and an international culture of responsibility around research involving pathogens.

The U.S. government, often in concert with the NSABB, has been engaged with the international community for many years and continues to work with those governments and organizations actively considering GOFROC-related issues. Presentations to the NSABB, its working groups, and at the National Academies meetings provided perspectives about the activities of foreign governments, international organizations, researchers, and others, and greatly aided the NSABB during the development of this report.

[58] National Academies of Sciences, Engineering, and Medicine. 2016. *Gain of Function Research: Summary of the Second Symposium, March 10-11, 2016*. Washington, DC: The National Academies Press. doi: 10.17226/23484.
[59] *Gain of function: experimental applications relating to potentially pandemic pathogens*. European Academies Science Advisory Council, EASAC policy report 27, October 2015. http://www.easac.eu/
[60] *Summary report: Dual Use Research On Microbes: Biosafety, Biosecurity, Responsibility.* December 10 – 12, 2014, Herrenhausen Palace, Hanover, Germany. https://www.volkswagenstiftung.de/dualuseresearch
[61] *France-US Bilateral Workshop on Dual Use Research Issues: Summary Report*, February 11, 2016. U.S. Department of State.
[62] Draghia-Akli, Ruxandra, Director of the Health Directorate at the Research DG, European Commission, presentation to NSABB working group, July 23, 2015.
[63] Donker, Marianne, Ministry of Health, Welfare and Sport, Netherlands, presentation to NSABB working group, July 23, 2015.

6. Recommendations of the NSABB

Based on its analyses and findings, the NSABB developed the following recommendations (Box 3) to the U.S. government.

Box 3. Summary of Recommendations of the NSABB

Recommendation 1. Research proposals involving GOF research of concern entail significant potential risks and should receive an additional, multidisciplinary review, prior to determining whether they are acceptable for funding. If funded, such projects should be subject to ongoing oversight at the federal and institutional levels.

Recommendation 2. An advisory body that is designed for transparency and public engagement should be utilized as part of the U.S. government's ongoing evaluation of oversight policies for GOF research of concern.

Recommendation 3. The U.S. government should pursue an adaptive policy approach to help ensure that oversight remains commensurate with the risks associated with the GOF research of concern.

> **Recommendation 3.1.** The U.S. government should develop a system to collect and analyze data about laboratory safety incidents, near-misses, and security breaches as well as the effectiveness of mitigation measures to inform GOF research of concern policy development over time.
>
> **Recommendation 3.2.** The U.S. government should develop or facilitate the development of a system to collect and analyze data about Institutional Review Entity (IRE) challenges, decisions, and lessons learned to provide feedback to the IRE community and to inform policy development for GOF research of concern over time.

Recommendation 4. In general, oversight mechanisms for GOF research of concern should be incorporated into existing policy frameworks when possible.

Recommendation 5. The U.S. government should consider ways to ensure that all GOF research of concern conducted within the U.S. or by U.S. companies be subject to oversight, regardless of funding source.

Recommendation 6. The U.S. government should undertake broad efforts to strengthen laboratory biosafety and biosecurity and, as part of these efforts, seek to raise awareness about the specific issues associated with GOF research of concern.

Recommendation 7. The U.S. government should engage the international community in a dialogue about the oversight and responsible conduct of GOF research of concern.

Recommendation 1. Research proposals involving GOF research of concern entail significant potential risks and should receive an additional, multidisciplinary review, prior to determining whether they are acceptable for funding. If funded, such projects should be subject to ongoing oversight at the federal and institutional levels.

GOFROC entails the generation of pathogens—perhaps novel pathogens—with anticipated pandemic potential. The risks associated with such studies are uncertain but potentially significant. It is possible that generating a laboratory pathogen with pandemic potential introduces a risk of a pandemic, albeit a low probability risk, that did not exist before that pathogen was generated. Therefore, a new, pre-funding review and approval mechanism is warranted before such studies should be undertaken. The NSABB's proposed conceptual approach for guiding funding decisions about GOFROC entails identifying GOFROC and subjecting such studies to an additional pre-funding review and approval process. The attributes that describe GOFROC, the principles that should guide funding decisions for GOFROC, and the steps in a proposed review/approval process for GOFROC are described below.

Identifying GOF research of concern

GOFROC is research that can be reasonably anticipated to generate a pathogen with pandemic potential. Determining whether a proposed research project is likely to do so will entail uncertainty and will require scientific and other expert judgment.

To be considered GOFROC, the research must, in a single step or over the course of multiple manipulations, be reasonably anticipated to generate a pathogen with both of the following attributes:

i. **The pathogen generated is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations.** To be considered "highly transmissible" the pathogen must be judged to have the capacity for sustained secondary transmission among humans, particularly, but not exclusively, by the respiratory route. Such a determination might be informed by data describing human infections by naturally-circulating isolates of the pathogen or studies in relevant experimental mammalian models that serve as a proxy for human infections. To be considered "capable of wide and uncontrollable spread in human populations" it must be judged that there would be limited options for controlling the spread of the pathogen other than patient isolation or quarantine. Such a determination might be made, for instance, if humans lack population immunity to the resulting pathogen, if the pathogen would evade or suppress the human immune response, if the pathogen would be resistant to medical countermeasures, or if existing countermeasures would be unavailable globally in sufficient quantities.

AND

ii. **The pathogen generated is likely highly virulent and likely to cause significant morbidity and/or mortality in humans.** To be considered "highly virulent" the pathogen must be judged to have the capacity for causing significant consequences in humans, such as severe disease and/or a high case fatality rate. Such a determination might be informed by data describing human infections by naturally-circulating strains of the pathogen or studies in relevant experimental mammalian models that serve as a proxy for human disease.

Any study involving the generation of a pathogen exhibiting the two attributes above would be considered GOFROC. However, it is generally anticipated that the following types of activities would not be considered GOFROC:

- Studies to characterize the virulence and transmission properties of circulating pathogens
- Surveillance activities, including sampling and sequencing
- Activities associated with developing and producing vaccines, such as generation of high-growth strains

Importantly, a proposed experiment need not involve the simultaneous enhancement of both phenotypes. Thus, research involving a naturally-occurring pathogen that exhibits one of the above attributes would be considered GOFROC if a study were anticipated to confer the second attribute to the agent (while retaining the first attribute). Other studies may generate a pathogen with the above attributes after a series of manipulations that enhance the phenotypes separately but ultimately result in a pathogen with both attributes. Any route of experimentation that is anticipated to ultimately generate a pathogen that exhibits both of the characteristics above would be considered GOFROC and should be reviewed carefully before it can be funded.

Appendix C describes examples of studies that would and would not be considered GOFROC. These examples are provided as general guidance. A more detailed consideration of the specific characteristics of a pathogen in question as well as the proposed experimental manipulations would be required to determine whether a research proposal is GOFROC.

Pre-funding review and approval of GOF research of concern

Proposals anticipated to involve GOFROC should be subject to additional review prior to making a funding decision and to substantial federal oversight throughout the course of the research, if funded. The NSABB developed principles that should guide the review and funding of these proposals. There should be a high degree of confidence that a study will be conducted in accordance with these principles before determining that the proposal is suitable for funding. Studies that cannot be or are not anticipated to be conducted in accordance with the principles below should not be funded.

Principles for guiding review and funding decisions

Only projects that are in line with **all of the following principles** should be considered acceptable for funding. The principles below are intended to embody the substantive ethical values described in section 4.2 and the process of applying these principles would involve scientific, security, ethical, and other considerations.

i. **The research proposal has been evaluated by a peer-review process and determined to be scientifically meritorious, with high impact on the research field(s) involved.** If GOFROC is to be funded and conducted it must first and foremost address a valuable scientific question or public health need.

ii. **The pathogen that is anticipated to be generated must be judged, based on scientific evidence, to be able to arise by natural processes.** It is difficult to predict the types of pathogens that can or will emerge in nature. Nevertheless, before a pathogen with pandemic potential is generated through laboratory manipulations it is essential to consider whether such a pathogen could arise in nature. GOFROC may be permissible if the study were to generate a pathogen that is anticipated to arise in nature or if the study were to provide insight into natural evolutionary processes. GOFROC would not be permissible if it were to generate a laboratory pathogen that is highly unlikely to arise in nature.

iii. **An assessment of the overall potential risks and benefits associated with the project determines that the potential risks as compared to the potential benefits to society are justified**. Prior to funding GOFROC, the anticipated risks and potential benefits must be carefully evaluated. In general, the potential benefits associated with a research project should be commensurate with or exceed the presumed risks. Projects involving significant risks and little anticipated benefits are ethically unacceptable and should not be funded. If the potential risks appear high, the possible benefits should also appear high. Risks should be managed and should be mitigated whenever possible. The extent to which risks can be mitigated should factor into the assessment.

iv. **There are no feasible, equally efficacious alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach.** Alternative approaches must be explored and critically examined before funding GOFROC. It is possible that the proposed experimental approach that raises concern is the only feasible approach for addressing the scientific question at hand. In other cases, modifications of the experimental design, use of attenuated or other strains that pose fewer risks to humans, or different approaches with less risk that may provide the same information may be feasible. Lines of experimentation that entail less risk should be pursued whenever possible.

v. **The investigator and institution proposing the research have the demonstrated capacity and commitment to conduct it safely and securely, and have the ability to respond rapidly and adequately to laboratory accidents and security breaches.** Prior to funding, the risks associated with proposed GOFROC must be identified and assessed, and clear, realistic plans for managing risks should be developed. In order to manage risks associated with GOFROC, an institution must have adequate facilities, resources, security, trained personnel, administrative structures, ongoing occupational health and safety monitoring procedures,

relationships with local public health authorities and first responders, and the ability to adapt to unanticipated situations by increasing containment or adding additional safety or security features. In addition to adhering to standards of compliance, an institution (and the investigators proposing the study) should have a demonstrated commitment to laboratory safety and security, scientific integrity, and the responsible conduct of research. The researchers and institution should be committed to a culture of responsibility, perhaps demonstrated through adherence to a formal code of conduct or other measures.

vi. **The results of the research are anticipated to be broadly shared in compliance with applicable laws and regulations in order to realize their potential benefits to global health.** Prior to funding GOFROC, consideration should be given to the type of research-related information and products that are likely to be generated. The research-related information and products are expected to be shared appropriately and a responsible communication plan should be developed at the outset, as appropriate. NSABB[64] and the U.S. government[65] have issued guidance for developing communication plans for dual use research of concern that include consideration of the content, timing, and distribution of the research information.

vii. **The research will be supported through funding mechanisms that allow for appropriate management of risks and ongoing federal and institutional oversight of all aspects of the research throughout the course of the project.** GOFROC should be funded through mechanisms that ensure appropriate biocontainment conditions are utilized, adequate biosecurity precautions are in place, and that the data and materials generated will be shared appropriately. The funding mechanism should allow for modification of required mitigation and oversight features, as well as research objectives during the course of the research, if needed.

viii. **The proposed research is ethically justifiable.** Determinations of whether proposed GOFROC should be undertaken involve value judgments to assess whether any potential risks are justified. Non-maleficence, beneficence, justice, respect for persons, scientific freedom, and responsible stewardship are among the values that should be considered when ultimately making decisions about whether to fund GOFROC.

[64] Appendix 5, *Proposed Framework for the Oversight of Dual Use Research Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information*. National Science Advisory Board for Biosecurity, June 2007.
[65] Section E, *Tools for the Identification, Assessment, Management, and Responsible Communication of Dual Use Research of Concern: A Companion Guide to the United States Government Policies for Oversight of Life Sciences Dual Use Research of Concern.* U.S. government, September 2014.

The Review Process for Proposals Involving GOF Research of Concern

The NSABB proposes the following conceptual approach for guiding funding decisions about GOFROC (Figure 5). Review of research projects that may involve GOFROC would involve five steps:

1. Investigators and research institutions identify proposed GOFROC, as described by the two attributes for identifying GOFROC.
2. Funding agencies identify or confirm proposed GOFROC.
3. A Department-level panel of U.S. government experts reviews proposals involving GOFROC to determine whether the proposal meets the 8 principles for guiding funding decisions and to make recommendations as to whether the proposed research is acceptable for funding.
4. Funding agencies make a funding decision, and if the proposal is funded, establish risk mitigation plans and issue the funding award with appropriate terms and conditions to help ensure ongoing oversight.
5. Investigators and institutions conduct the research in accordance with any applicable federal, state, and local oversight policies and employ any necessary additional mitigation strategies. Federal agencies provide oversight to ensure adherence to established risk mitigation plans and funding terms.

Investigators and institutions identify GOFROC (Step 1). Prior to submission of an application for funding, investigators and research institutions should identify possible GOFROC and submit with the research proposal any relevant information such as plans for biosafety, biosecurity, and coordination with local and/or state public health and safety officials in the event of an accident or theft; descriptions of facilities available; a justification for the proposed approach that considers possible non-GOFROC alternatives that have been considered; and a discussion of the value and potential benefits of the proposed research. Identification of possible GOFROC should not affect a subsequent federal scientific merit review either positively or negatively.

A need for guidance to investigators and institutions. The U.S. government should develop a "Points to Consider" document to provide guidance to investigators and institutions when preparing research proposals that may involve GOFROC. Such a document would describe any requirements for proposals involving GOFROC and provide guidance on the type of information that should be included in a proposal to facilitate its review. This document should be reviewed and updated as necessary.

Agency and Department-level review of GOFROC (Step 2 & 3). After the standard funding agency scientific merit review process, proposals that are determined to be scientifically meritorious and likely to be favorably considered for funding would also be reviewed by the funding agency (Step 2) to determine if they constitute GOFROC. Prior to being determined acceptable for funding, proposals identified by a funding agency as involving GOFROC would require an additional, higher level, Departmental review (Step 3). If a proposal does not involve GOFROC, it would proceed along the normal pathway for further evaluation and funding decisions.

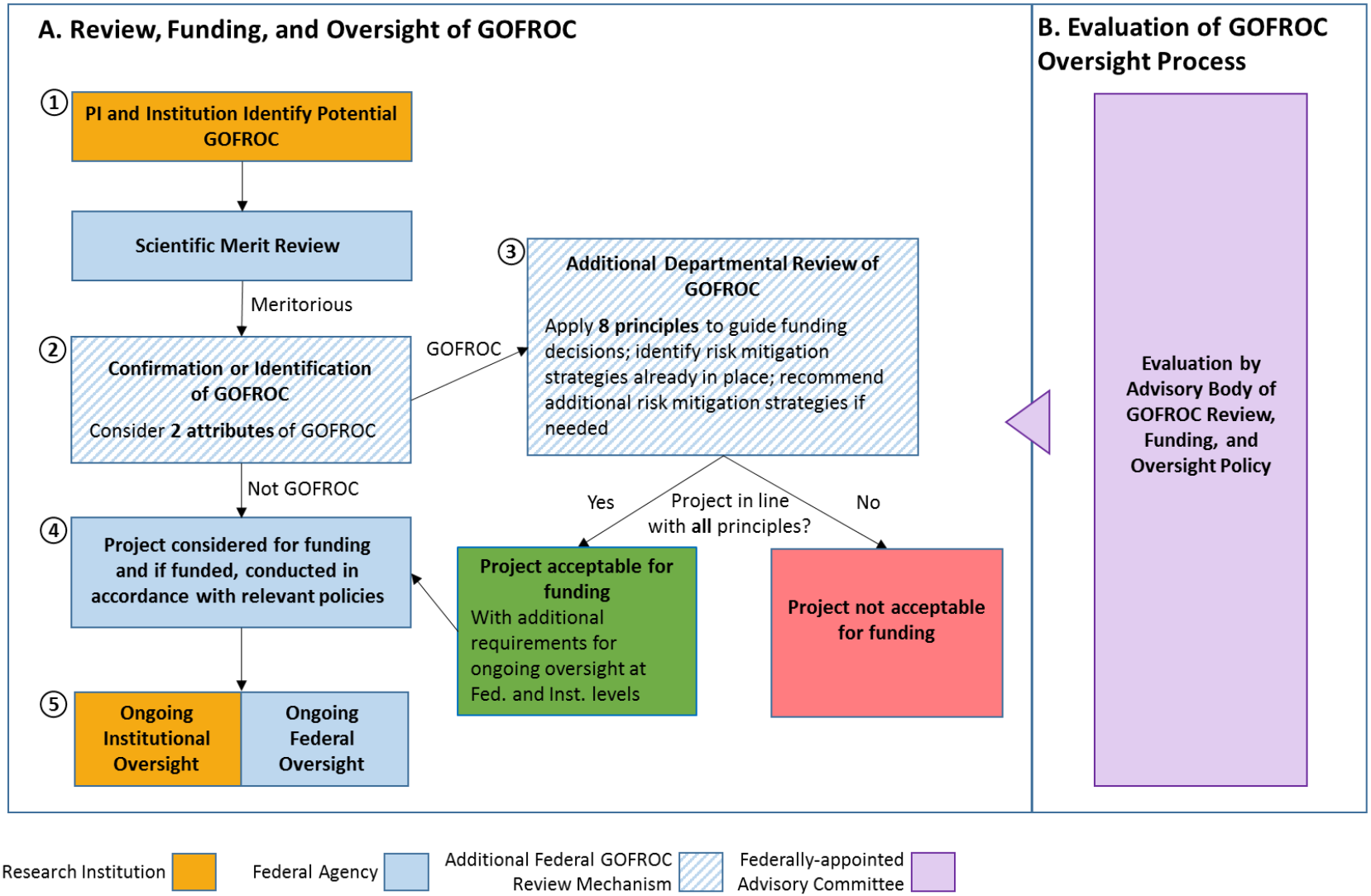

Figure 5. Proposed approach for the oversight of GOF research of concern. A) A conceptual approach for the identification, review, funding, and ongoing oversight of GOF research of concern. B) A Federally-appointed advisory committee would periodically evaluate the policies and processes developed for funding and providing oversight for GOFROC.

The additional review of proposals involving GOFROC would determine whether the proposed research aligns with the 8 principles to guide funding decisions. Applying these principles will help to ensure that the GOFROC is scientifically and ethically acceptable, that the risk-benefit balance is favorable, that alternative approaches are explicitly considered, and that the research can be performed safely and securely. It is envisioned that the additional review of proposals involving GOFROC would involve diverse, multidisciplinary expertise including scientific, public health, biosafety, national security and intelligence, legal, bioethics, and other perspectives. To the extent possible, the Departmental review process should be efficient, well-documented, and adaptive. In addition, the process should be structured to avoid real or apparent conflicts of interest and to provide consistency across USG agencies that might fund GOFROC. It is also envisioned that research institutions proposing the GOFROC might be asked for, and would have an opportunity to provide, any additional information that might be necessary for a thorough and substantive review of the research proposal. The NSABB also recommends (see Recommendation 2) that an advisory body that is designed for transparency play a role in the evaluation of the oversight policies for GOFROC.

Funding decision and risk mitigation (Step 4). During the course of the Department-level review, the relevant risk management plans should be critically evaluated and additional risk mitigation measures may be recommended in order for GOFROC to be considered acceptable for funding. A satisfactory risk management plan would entail appropriate biocontainment facilities and biosafety practices, appropriate standard operating procedures and administrative controls, occupational health and safety programs and security systems for protecting laboratory strains and reagents, and promoting personnel reliability. Some or all of the additional risk mitigation measures listed in Box 4 may also be recommended. Section 6.3 in Gryphon's RBA report also describe additional safety measures that many laboratories performing GOFROC have employed. These and a variety of additional measures could be required as conditions of funding.

Box 4. Additional risk mitigation measures to be employed, as appropriate, for GOF research of concern.

Risk mitigation features that should be considered prior to funding GOFROC include requirements to:

- Provide additional training to researchers
- Enhance biosafety practices or features, as warranted given the specific strains and proposed manipulations
- Enhance security measures around strains, reagents, notebooks, and personnel
- Prohibit certain additional GOFROC experiments without prior approval
- Treat the research as if subject to the USG DURC policies, if it is not already
- Conduct more frequent institutional biosafety and biosecurity reviews of the research
- Require more frequent progress reports and discussions with federal funding agency staff, particularly about unanticipated results that may raise concerns
- Conduct periodic site inspections/evaluations, if not already required
- Identify certain experimental outcomes that would trigger a re-evaluation of the risks and benefits prior to proceeding with a study
- Develop a responsible communication plan, specifically, including a description of biosafety and biosecurity practices that were employed for the research
- Communicate regularly and coordinate with federal, state, and local public health and safety officials on accident and theft response
- Conduct bioethics consultations at the local and federal level throughout the life cycle of the research
- Develop and/or adhere to an appropriate code of conduct

Ongoing oversight (Step 5). Finally, throughout the course of the funding, both federal and institutional oversight are critically important. The project should be carefully monitored to ensure that required conditions are met, that the principles guiding the decision to fund are still satisfied, and that any changes, significant developments, and publication/communication plans are discussed and addressed in a timely manner.

Recommendation 2. An advisory body that is designed for transparency and public engagement should be utilized as part of the U.S. government's ongoing evaluation of oversight policies for GOF research of concern. An advisory mechanism, such as a committee governed by the Federal Advisory

Committee Act[66], would allow for an independent examination of the U.S. government's policies for reviewing, funding, and conducting GOFROC (Figure 5.B.). Such a group could evaluate the additional review and funding processes for GOFROC to understand how decisions were made, identify challenges to implementing the policy, and provide recommendations, as needed. Importantly, this mechanism would also provide transparency, promote public engagement, and would facilitate continued dialogue about GOFROC.

Recommendation 3. The U.S. government should pursue an adaptive policy approach to help ensure that oversight remains commensurate with the risks associated with the GOF research of concern. The risk/benefit profile for GOFROC may change over time and should be re-evaluated periodically to ensure that the risks associated with such research are adequately managed and the benefits are being realized. An adaptive approach to the oversight of GOFROC would entail the continual evaluation of the risks and benefits associated with the research, as well as the burdens and effectiveness of the additional proposal review process and ongoing oversight measures. An adaptive approach would allow policymakers to learn from experience and update policies accordingly as the risk/benefit landscape changes. For instance, the risks associated with a research proposal or project may change if newly developed countermeasures become available or if new information emerges to clarify certain risks or enable certain benefits.

Recommendation 3.1. The U.S. government should develop a system to collect and analyze data about laboratory safety incidents, near-misses, and security breaches as well as the effectiveness of mitigation measures to inform GOF research of concern policy development over time. Examining such data would provide a better understanding of the risks, inform future risk assessments, and allow for the refinement of oversight policies over time.

Recommendation 3.2. The U.S. government should develop or facilitate the development of a system to collect and analyze data about Institutional Review Entity (IRE) challenges, decisions, and lessons learned to provide feedback to the IRE community and to inform policy development for GOF research of concern over time. Examining such data would provide a better understanding of the effectiveness and consistency of policy implementation and support local IRE decision-making.

Recommendation 4. In general, oversight mechanisms for GOF research of concern should be incorporated into existing policy frameworks when possible. Any additional oversight of GOFROC should be built into existing mechanisms rather than having the U.S. government develop a novel policy specific to GOFROC. Adapting or harmonizing current policies is preferable to developing entirely new oversight frameworks or wholly new approaches to manage the risks associated with these studies. There are precedents for additional Department-level pre-funding review of certain GOF studies (i.e.

[66] *Federal Advisory Committee Act*. http://www.gsa.gov/portal/content/100916

HHS Framework) as well as mechanisms for higher-level review and approval of certain studies (i.e., Major Actions, under the *NIH Guidelines*; restricted experiments, under the Select Agent Program). There are also mechanisms for continual Federal-level monitoring of biosafety and biosecurity risks for individual projects (i.e., USG Policy for Federal Oversight of DURC, select agent program) and established mechanisms for ongoing institutional oversight (i.e., IREs under the USG Policy for Institutional Oversight of Life Sciences DURC; IBCs under the *NIH Guidelines*). Wherever possible, these mechanisms should be employed to ensure the initial and ongoing oversight of GOFROC.

Importantly, not all GOFROC would necessarily be subject to the entire suite of U.S. oversight policies. For instance, some studies involving pathogens not included in the USG policies for DURC oversight or not on the select agent list could generate a pathogen with pandemic potential. Additional oversight measures may need to be stipulated at the time of funding for GOFROC proposals that are not subject to sufficient existing oversight. For instance, specific, enhanced containment practices may be required, or a project may require ongoing monitoring at the federal and institutional levels for its potential to be DURC. Box 4 describes a number of risk mitigation measures for GOFROC that could be implemented, potentially by leveraging existing policy frameworks.

Recommendation 5. The U.S. government should consider ways to ensure that all GOF research of concern conducted within the U.S. or by U.S. companies be subject to oversight, regardless of funding source. GOFROC conducted in the U. S. that is funded by the U.S. government or through private funding sources should be subject to equivalent oversight to ensure that the associated risks are adequately managed. The USG should consider ways to introduce oversight not only as a term and condition of a funding award but also via other mechanisms that would enable oversight of all relevant research activities, regardless of the funding source.

Recommendation 6. The U.S. government should undertake broad efforts to strengthen laboratory biosafety and biosecurity and, as part of these efforts, seek to raise awareness about the specific issues associated with GOF research of concern. Current discussions about GOFROC relate to broader domestic and international discussions about laboratory safety and security. A “top down” approach to managing the risks associated with GOFROC through federal policies and oversight is appropriate. However, top-down approaches alone, in the form of federal and/or institutional policies and leadership, will likely not be sufficient. It is also critical to have adequately trained personnel that value safe and secure laboratory environments for conducting GOFROC. Therefore, it will also be important to facilitate a “bottom up” approach whereby scientific leaders and professional societies, as well as research staff involved in the design and conduct of GOFROC, are educated about biosafety, biosecurity, and the responsible conduct of their research. The U.S. government should engage the research community with the goal of promoting a culture of responsibility, or “scientific citizenship,” whereby all participants in the research enterprise have a sense of shared responsibility. Such a culture would

incorporate and stress the values of safety, security, compliance, and bioethics, and would work to promote public trust in the scientific enterprise.

Recommendation 7. The U.S. government should engage the international community in dialogue about the oversight and responsible conduct of GOF research of concern. Life sciences research is a global endeavor that continues to grow as more countries invest in their research capacities and as scientists move and collaborate across national boundaries. Life sciences research enables biomedical breakthroughs, pandemic preparedness, public health response efforts for emerging infectious diseases, and also provides an important economic driver. As more investigators undertake research involving pathogens, however, the associated risks become more likely to have international implications. The risks associated with GOFROC are notably international in nature since laboratory accidents or the deliberate misuse of pathogens with pandemic potential could have global consequences. Laboratories anywhere can undertake GOFROC, and publications in the open scientific literature may enable others to generate pathogens with pandemic potential.

NSABB has benefitted greatly from the extensive input into its deliberations by experts representing foreign governments, international organizations, academia, and others during presentations and comments at its meetings and the National Academies symposia.

The U.S. government should continue to engage the international community on issues related to dual use research, including policies, oversight mechanisms, science, research conduct, biosafety, biosecurity, containment, publication, funding, and bioethics. These issues are important in general and are particularly relevant to GOFROC. The U.S. government's international engagement efforts should seek to promote a global culture of responsibility and enhance the quality, legitimacy and effectiveness of oversight processes.

The U.S. government should build these efforts on the substantial international engagement activities that it and the NSABB have carried out since the NSABB was established. Such efforts have included three international roundtable meetings on dual use research issues, a series of webinars focusing on different global regions, and an international consultative workshop on GOF issues[67]. In addition, the U.S. National Academies and the European Academies Science Advisory Council have been engaged in the recent policy debates involving GOF studies and may be well positioned to continue international dialogue on the issue in coordination with national governments and relevant international organizations. The USG is encouraged to participate in such activities.

[67] Information about these meetings and activities, including agendas, summaries, and archived videocasts, can be found on the NSABB website at: http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/nsabb/nsabb-meetings-and-conferences/international-engagement

7. Appendices

Appendix A. Description of NSABB Deliberations

NSABB Deliberations

The NSABB established two working groups to accomplish the two portions of its charge, which were to result in discrete work products.

- **Deliverable 1.** A report conveying NSABB's advice on the design, development, and conduct of the risk and benefit assessments.
- **Deliverable 2.** A report conveying NSABB's formal recommendations on the conceptual approach to the evaluation of proposed GOF studies.

DELIVERABLE 1: ADVISING ON THE RISK AND BENEFIT ASSESSMENTS

The first NSABB working group was tasked with advising on the design and conduct of the risk and benefit assessments. The group met between December 2014 and April 2015 and was consisted of 13 NSABB voting members as well as non-voting *ex officio* members and other *ad hoc* members from Federal agencies. The group convened by telephone conference calls and held a one-day in-person meeting.

The working group developed a draft *Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research*, which was presented to the full NSABB and developed further based on input from all Board members. The final framework was approved by the full Board on May 5, 2015 and is included in this report as Appendix H. The recommendations in this framework were intended to inform the NIH as it guided the work of Gryphon Scientific in its risk and benefit assessments of GOF research. The aim of the NSABB's framework was to help generate risk and benefit assessments that would provide information that would allow the NSABB to make sound, evidence-based recommendations.

The NSABB recommended that the RBA focus on studies involving influenza viruses (seasonal strains, as well as high and low pathogenic avian strains) and SARS and MERS coronaviruses. Given that most pandemics are associated with respiratory transmission, pathogens capable of airborne transmission were considered to be of most acute concern. NSABB recognized that the RBA would provide information specific to the pathogens and scenarios that were examined, but intended that the assessments would generate information that could be more broadly interpreted and applied. Thus, NSABB's recommended approach to the assessments was intended to align with the USG's October 2014 statement, which states that while "gain-of-function studies that fall within the scope of research subject to the funding pause will be a starting point for deliberations, the suitability of other types of gain-of-function studies will be discussed."

DELIVERABLE 2: RECOMMENDATIONS ON A CONCEPTUAL APPROACH FOR EVALUATING PROPOSED GOF STUDIES

The second NSABB working group was tasked with developing draft recommendations on the conceptual approach for the evaluation of proposed GOF studies. The group met between June 2015 and May 2016 and consisted of 18 NSABB voting members as well as non-voting *ex officio* members and other *ad hoc* members from Federal agencies; (Appendix F). The group convened by telephone conference calls and met twice in person.

In addition to the working group's primary task of developing draft recommendations, it continued to provide input on the conduct of the risk and benefit assessments. The working group also received periodic status updates on the RBA from NIH and Gryphon, as well as reports on the commissioned ethics analysis by Dr. Michael Selgelid, examined draft work products, and reported back to the full NSABB.

In developing draft recommendations on a conceptual framework for evaluating proposed GOF studies, the working group structured its deliberations into three phases.

Phase I. Policy examination, research, and information gathering
Phase II. Interpretation, analysis, and synthesis of information and results
Phase III. Development of recommendations

In Phase I the working group sought to 1) identify and examine the information necessary to inform development of recommendations and 2) begin to identify principles that should guide the development of NSABB recommendations. The working group began its deliberations by considering the topic areas discussed at the NSABB meeting in May 2015, which included examination of relevant U.S. and international policy and consideration of broader perspectives such as those from funding agencies, national security experts, journal editors and scientific publishers, ethicists, and others. The working group held an in-person meeting to consult with experts on many of these topics. The working group also examined a number of published GOF studies and discussed how current policies might apply to such studies to provide oversight and risk mitigation.

During Phase II the working group focused on translating information about risks and benefits as well as ethics into decisions and recommendations. It examined how current policies apply to GOF studies and began to develop preliminary observations and findings. The working group discussed the ethical issues associated with funding and conducting GOF studies, particularly noting the values and ethical decision-frameworks that might be applied to policy decisions about GOF studies. The working group also developed analytic tools to assist it in systematically analyzing the results of the risk and benefit assessments. In November 2015, the working group began receiving briefings from Gryphon conveying the results of the RBA, as well as reports on ethics from Dr. Selgelid. The group sought to identify GOF

studies that might raise particular concerns and may require additional oversight or consideration prior to being funded.

In Phase III the working group developed its draft recommendations based on its analysis of the risk and benefit assessments and the ethics report, and consideration of all other information and perspectives that were examined.

Deliberations by the Full NSABB

The full NSABB convened times 6 times between October 2014 and May 2016. At these meetings the NSABB working groups provided progress updates and the full Board, deliberated the issues further, consulted with various experts, and sought public feedback. Public comments made at NSABB meetings and delivered to the NSABB in writing were carefully considered by the Board during its deliberations. The articles, resources, and stakeholders consulted by the NSABB and its working groups throughout this process are listed in Appendix E.

On November 25, 2014, NSABB voted to approve a statement conveying to the USG concerns it heard regarding the implementation of the funding pause for certain GOF studies.[68] On May 5, 2015, NSABB voted to approve its *Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research*.[69] On May 24, 2016, NSABB voted to approve its *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research* (this document).

Role of the National Academies in the Deliberative Process

The National Academies played a critical role in the ongoing deliberative process. The National Research Council and the Institute of Medicine (now National Academy of Medicine) were asked to convene two forums to engage the life sciences community and to solicit feedback from scientists, the public, and other stakeholders. These forums involved discussion of principles important for the design of RBA of GOF research and of NSABB draft recommendations.

The first National Academies workshop was held on December 15 & 16, 2014 and focused on the potential risks and benefits associated with GOF studies, ways to assess risks and benefits, strengths and limitations of risk-benefit analyses, and the ethical and policy implications associated with funding and

[68] *Statement of the National Science Advisory Board for Biosecurity Regarding the USG Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses*. National Science Advisory Board for Biosecurity, November 25, 2014.
http://osp.od.nih.gov/sites/default/files/resources/Final%20NSABB%20Funding%20Pause%20Statement_12-12-14_0.pdf
[69] *Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research*. National Science Advisory Board for Biosecurity, May 5, 2015.
http://osp.od.nih.gov/sites/default/files/resources/NSABB_Framework_for_Risk_and_Benefit_Assessments_of_GOF_Research-APPROVED.pdf

conducting GOF studies that have raised concerns.[70] The discussions at this meeting directly informed the development of NSABB recommendations for conducting the RBA and its subsequent deliberations. In particular, the discussions about the potential risks and benefits associated with GOF studies informed NSABB's recommendations for the types of risks and benefits that should be analyzed by Gryphon. A common theme at this National Academies meeting was that the term "gain-of-function" is too broad and that in fact, only a subset of GOF studies truly raise concerns. NSABB applied this insight to its subsequent analysis of the RBA by seeking to identify the subset of GOF studies that raised significant or unique concerns. Finally, the legal and policy discussions that were initiated at this meeting prompted the NSABB to explore these topics, as well as ethical issues, further.

The second National Academies meeting was held on March 10 & 11, 2016 and included a discussion of the completed RBA and NSABB's preliminary findings and draft recommendations. NSABB's proposed attributes for identifying GOFROC were a major discussion point at this meeting, which resulted in NSABB refining and clarifying these attributes. In addition, there was significant discussion about the desirability of an adaptive policy approach, the need for data to inform policy decisions, and the role that a federal advisory committee might play in evaluating GOFROC or GOFROC policy. This meeting also had a significant focus on international issues and perspectives, with specific discussion of ongoing and potential future international activities in this area.[71]

The Risk and Benefit Assessments of GOF Studies

NIH commissioned Gryphon Scientific to perform formal risk and benefit assessments to provide the NSABB with qualitative and quantitative information about the risks and benefits associated with conducting certain GOF studies. Dr. Rocco Casagrande, the principal investigator for the study, presented to the NSABB on May 5, 2015 an overview of Gryphon's approach to conducting the RBA, which included a quantitative biosafety risk assessment, a semi-quantitative biosecurity risk assessment, and a qualitative benefit assessment. Prior to voting to finalize its *Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research*, NSABB discussed with Dr. Casagrande its draft recommendations and how Gryphon's proposed approach aligned with NSABB's proposed recommendations. In June 2015, Dr. Casagrande presented and discussed a more detailed work plan with the NSABB working group. Over the course of the study, the NSABB working group received occasional progress reports from Gryphon and NIH staff, and were provided draft sections of the RBA as they became available. In November 2015 the NSABB working group began receiving the results of the completed RBA. A draft version of the report was posted in advance of the January 2016 NSABB meeting. Gryphon's final report was made publicly available in April, 2016.[72]

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[70] National Research Council and the Institute of Medicine of the National Academies. 2015. *Potential Risks and Benefits of Gain-of-Function Research: Summary of a Workshop, December 15 & 16, 2014*. Washington, DC: The National Academies Press. doi: 10.17226/21666.

[71] National Academies of Sciences, Engineering, and Medicine. 2016. *Gain of Function Research: Summary of the Second Symposium, March 10-11, 2016*. Washington, DC: The National Academies Press. doi: 10.17226/23484.

[72] *Risk and Benefit Analysis of Gain-of-Function Research, Final Report*. Gryphon Scientific, April 2016. http://www.gryphonscientific.com/wp-content/uploads/2016/04/Risk-and-Benefit-Analysis-of-Gain-of-Function-Research-Final-Report.pdf

The NIH Office of Science Policy managed the contract with Gryphon Scientific. NIH staff met weekly with Gryphon to accomplish the goals of the Statement of Work and to ensure the recommendations provided in the NSABB's *Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research* continued to inform the conduct of the RBA, as appropriate. NIH staff also consulted with NSABB *ex officio* members to get broader expertise and advice, and to help ensure that the risk and benefit assessments yielded information that would inform subsequent policy deliberations by the U.S. government.

Considering Ethical Issues Associated with GOF Studies

To guide the NSABB's evaluation of the risks and benefits associated with GOF studies and its development of recommendations, the Board sought additional input and analysis on ethics. NIH commissioned Dr. Michael Selgelid, Monash University, to examine the literature regarding the ethical issues associated with funding and conducting GOF research and to explore different ethical frameworks that might be utilized when considering how to evaluate the potential risks and benefits associated with GOF studies. Dr. Selgelid was also asked to provide an ethical decision-making framework that NSABB could consider using when analyzing the information provided in the risk and benefit assessments of GOF studies. The decision framework was to identify and consider ethical values that may not be fully captured by a RBA. Dr. Selgelid's analysis was to be accomplished in a neutral, objective manner, without making any definitive recommendations on whether and how to fund or conduct certain GOF studies or what policy course might be the most appropriate. Dr. Selegelid presented his initial work to the NSABB in September 2015 and delivered to the NIH a draft paper in December 2015, which was conveyed to the NSABB and made publicly available. A final version of the paper was made publicly available in April 2016.[73]

[73] Selgelid, M., *Gain-of-Function Research: Ethical Analysis*. April 2016. http://osp.od.nih.gov/sites/default/files/Gain_of_Function_Research_Ethical_Analysis.pdf

Appendix B. Summary of U.S. Policies for Biosecurity and Biosecurity Oversight

Oversight Measures	Risks Addressed	Description of Oversight	Analysis/Applicability to GOF Studies
Biosafety in Microbiological and Biomedical Laboratories (BMBL), 5th Edition (December 2009) http://www.cdc.gov/biosafety/publications/bmbl5/index.htm	Biosafety risks	**Applies to:** Life sciences research involving infectious microorganisms or hazardous biological materials **Description:** General biosafety practices and biological containment for various classifications (risk groups) of microorganisms and etiological agents	BMBL does not describe GOF studies per se but does include summary statements and biocontainment guidance for research involving various influenza strains (including contemporary and non-contemporary human, high and low pathogenic avian, swine, the 1918 influenza strain, and reassortant viruses) and SARS-CoV. MERS-CoV had not emerged at the time of the last BMBL update but interim laboratory biosafety guidance was issued by CDC and is referenced by BMBL. BMBL is a guidance document and generally considered the authoritative reference for laboratory biosafety but it is not a regulatory document; compliance is voluntary.
NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (November 2013) http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines	Biosafety risks	**Applies to:** Basic or clinical life sciences research that involves recombinant or synthetic nucleic acid molecules and is conducted at an institution receiving NIH funding for any such research **Description:** Describes roles and responsibilities of institutions and investigators in safely conducting research. Requires institutional review with a focus on the concepts of risk assessment, risk group classification of agents, physical and biological containment levels, practices, personal protective equipment, and occupational health. **Advised by:** NIH Recombinant DNA Advisory Committee (RAC)	The NIH Guidelines have been amended to include additional guidance for work with Risk Group 3 influenza viruses (1918 H1N1, H2N2, highly pathogenic avian influenza (HPAI) H5N1) to specify enhancements to biosafety level 3 containment, practices, and occupational health requirements. NIH Guidelines were amended again to require further enhancements to facilities, biosafety equipment and practices, including occupational health practices, for research involving HPAI H5N1 strains transmissible among mammals by respiratory droplets. NIH Guidelines are often used as a model of biosafety guidance by the broader scientific community but compliance is required only by institutions receiving such funding from the NIH. The scope is also limited to research involving recombinant or synthetic nucleic acids. Some IBCs also review and approve non-recombinant pathogen research; however, not all institutions require their IBCs to do so.
HHS and USDA Select Agent Program (as of July 2014) http://www.selectagents.gov/regulations.html	Biosecurity (physical and personnel) and biosafety risks	**Applies to:** Biological agents and toxins that have the potential to pose a severe threat to public health and safety, based on a set of criteria. **Description:** Regulates the possession, use, and transfer of select agents and toxins. Overseen by the Federal Select Agent Program. Requires registration of individuals and entities; federal background investigations; federal review of restricted experiments; training; institutional compliance; etc. **Advised by:** Intragovernmental Select Agents and Toxins Technical Advisory Committee	Studies that could be considered GOF studies, which involve pathogens on the select agent list, are subject to oversight by the SAP. Researchers and institutions performing such studies must receive favorable security risk assessments by the FBI, register with the SAP, receive training on the proper procedures and practices for handling such agents, and abide by other aspects of the regulations. SARS-CoV, HPAI H5N1 influenza, and 1918 influenza viruses are select agents and GOF studies involving these pathogens are subject to oversight by the SAP. Restricted experiments that would entail conferring antiviral resistance to these viruses would require additional review and approval prior to being conducted. GOF experiments involving MERS, and other agents not included on the select agent list, would not be subject to oversight by the SAP.

USG Policy for Federal Oversight of DURC (March 2012) http://www.phe.gov/s3/dualuse/Pages/USGOversightPolicy.aspx	Biosecurity risks, particularly involving misuse of research information, products, and technologies (DURC)	**Applies to:** Life sciences research conducted at an institution receiving USG funding that involves any of 15 agents that pose the greatest risk of deliberate misuse with most significant potential for mass casualties or devastating effects.	The federal DURC policy requires identification and oversight of certain pathogen research involving 7 experimental types, some of which can be described as GOF experiments (i.e., enhancing the harmful consequences of an agent; increase transmissibility; alter host range; etc.) by Federal funding agencies. DURC policies only apply to research involving 15 pathogens. Institutions may review other studies for DURC potential but are not required to do so. Certain GOF studies that involve other agents would not be subject to DURC oversight under the policies.
USG Policy for Institutional Oversight of DURC (September 2014) http://www.phe.gov/s3/dualuse/Pages/InstitutionalOversight.aspx	Biosecurity risks, particularly involving misuse of research information, products, and technologies (DURC)	**Applies to:** Life sciences research conducted at an institution receiving USG funding that involves any of 15 agents that pose the greatest risk of deliberate misuse with most significant potential for mass casualties or devastating effects.	The institutional DURC policy requires federally-funded institutions to establish a system for the identification and oversight of certain pathogen research involving 7 experimental types, some of which can be described as GOF experiments (i.e., enhancing the harmful consequences of an agent; increase transmissibility; alter host range; etc.) DURC policies only apply to research involving 15 pathogens. Institutions may review other studies for DURC potential but are not required to do so. Certain GOF studies that involve other agents would not be subject to DURC oversight under the policies.
HHS Funding Framework for GOF studies (August 2013) http://www.phe.gov/s3/dualuse/Pages/HHSh5n1Framework.aspx	Biosafety and biosecurity risks associated with certain GOF experiments involving agents with pandemic potential	**Applies to:** Gain-of-function studies that are reasonably anticipated to generate HPAI H5N1 viruses that are transmissible, and LPAI H7N9 viruses that have increased transmissibility, between mammals by respiratory droplets **Description:** Describes an HHS Department-level review pre-funding review and approval process for certain GOF studies, which can result in funding, not funding, or funding with certain conditions and ongoing oversight.	The only policy focused specifically on funding decisions related to the types of GOF studies that have raised concerns. Narrowly focused only on specific GOF studies (enhancing mammalian transmissibility) on two avian influenza viruses; other GOF studies may raise concern and would not be reviewed under this framework.
USG Export Control Regulations http://www.bis.doc.gov/index.php/regulations/export-administration-regulations-ear		**Applies to:** Export or release of equipment, software and technology, chemicals, microorganisms, toxins, and other materials and information deemed dual use or strategically important to U.S. national security, economic, and/or foreign policy interests	Comprehensive set of federal regulations that control and restrict the export and release of sensitive equipment, software and technology; chemical, biological, and other materials and information as a means to promote national security interests and foreign policy objectives.

Appendix C. Identifying GOFROC: Examples of Studies that Would and Would Not be Considered GOFROC

Experiment that is anticipated to entail GOFROC and therefore require additional pre-funding review and approval	Rationale (See NSABB Rec. 1 for description of GOFROC Attributes)
An experiment that is anticipated to generate avian influenza viruses that are transmissible by the respiratory route in mammals, if the starting virus is highly virulent in humans.	**Attribute 1.** The experiment is anticipated to increase transmissibility by the respiratory route in a relevant experimental mammalian model. Further, altering the host range from birds to mammals could generate a virus to which there is no existing population immunity, resulting in a virus capable of wide and potentially uncontrollable spread among humans. **Attribute 2.** Since the starting virus is highly virulent in humans it can be reasonably anticipated that the resulting virus will remain highly virulent in humans.
Reassortant studies involving avian and human influenza virus strains conducted to identify reassortants with pandemic potential that could arise naturally.	**Attribute 1.** Given the starting viruses and the goal of the experiment to identify/select for reassortants that are potentially highly transmissible in mammals, it can be reasonably expected that one or more of the resulting strains could be highly transmissible in humans. Since the resulting viruses are reassortants between bird and human influenza viruses, it can be anticipated that the antigenicity of at least some will remain avian-specific such that human populations would not be expected to have been exposed to such a strain or have pre-existing immunity. Therefore, it can be anticipated that a resulting virus could be capable of wide and uncontrollable spread. **Attribute 2.** Whether or not any of the starting viruses are highly virulent in humans, it can be reasonably anticipated that the expression of novel combinations of gene segments, derived from different influenza strains, in reassortant viruses could result in a range of characteristics that includes high virulence.
Studies that would result in a strain of *Yersinia pestis* more likely to cause pneumonic forms of infection and be resistant to antibiotics.	**Attribute 1.** Given the ease of transmission of *Yersinia pestis* in previous pandemics, manipulations that would enhance its ability to spread by respiratory droplets and cause pneumonic infections would generate a highly transmissible pathogen. In addition, if this manipulation involved a strain that was resistant to frontline antibiotics, it can be anticipated that there would be limited options for controlling the spread of the pathogen among humans. **Attribute 2.** Since the starting agent is highly virulent in humans, particularly when spread through the respiratory route, it can be reasonably anticipated that the resulting agent will remain highly virulent in humans.

Experiment NOT anticipated to entail GOFROC and therefore not require additional pre-funding review and approval	Rationale
Studies aimed at generating a mouse-adapted MERS-CoV or other emerging human respiratory pathogen	**Not Attribute 1.** The starting virus is transmissible by the respiratory route among humans but is not highly transmissible. MERS-CoV transmission usually occurs as a result of close contact (e.g. providing unprotected care to an infected patient). Sustained community transmission has not been observed. Furthermore, the proposed adaptation to recapitulate human disease symptoms in mice would not be reasonably anticipated to enhance transmissibility thus the resulting virus would not be anticipated to be capable of wide and uncontrollable spread. **Possibly Attribute 2.** The starting virus is already highly virulent in humans and is associated with significant morbidity and mortality. However, it should also be noted that a mouse-adapted strain is likely to be less virulent in humans.
Studies enhancing the growth of seasonal influenza viruses, which may be performed during vaccine production	**Not Attribute 1.** The starting seasonal influenza virus is highly transmissible by the respiratory route in humans however, population immunity is likely to exist against circulating (and recently circulated) strains. Enhancement of growth is unlikely to result in a virus that can evade immunity, thus a virus capable of wide and uncontrollable spread would not be likely. **Possibly attribute 2.** Increasing seasonal virus' ability to replicate could potentially result in its increased ability to cause disease, which could result in highly virulent strains. **Note:** If this experiment were to involve an attenuated strain, as is often the case with vaccine production, it would be unlikely to result in a virus that is highly virulent in humans.
Antigenic drift studies whereby seasonal influenza viruses that are no longer neutralized by vaccine-induced immunity are generated and selected for in the laboratory.	**Not Attribute 1.** The starting seasonal influenza virus is highly transmissible by the respiratory route in humans. However, antigenic drift studies generate influenza viruses with some resistance to a specific immunization but do not change the antigenic character of the virus to a degree such that it would no longer be recognized by the human immune system. Given that the starting virus is a human virus—not one that naturally infects birds or other non-human hosts—there would likely be some pre-existing population immunity to the resulting strains. **Possibly attribute 2.** The experimental manipulation would not be anticipated to increase the virulence of the virus. The resulting strains are likely to exhibit a similar level of virulence as the starting strain. Whether its virulence is considered high or low would depend on the specific initial strain used.

Appendix D. Summaries of Stakeholder Perspectives

The NSABB consulted a wide range of experts and stakeholder groups including not only scientists and institutions that fund and conduct life sciences research, but a much larger and diverse array of groups including public health officials, medical practitioners, emergency responders, vaccine developers, scientific journals, as well as the general public, non-governmental organizations, individuals with international perspectives and others. To accomplish this, NSABB organized meetings with expert presentations and panels that offered opportunities for interested groups there and for individuals and organizations to express their views and contribute throughout the deliberative process in ways that have informed the NSABB deliberations. These include: several public full NSABB advisory committee meetings that included sessions dedicated to obtaining public comment, two public symposia hosted by the National Academies that obtained comments from the public at the meetings and online, as well as comments submitted to the NIH and NSABB by email, and discussions with subject matter experts during NSABB WG conference calls and in-person meetings. Also included below are views expressed in some of the articles that have been published on this topic. A complete list of the individuals consulted and articles examined by NSABB are listed in Appendix E. Gryphon also conducted extensive consultations with experts as part of their risk and benefit assessments of GOF research. Those experts are not listed here but a listing is available in Gryphon's report. [74]

The following is a synthesis of stakeholder ideas and opinions expressed during the deliberative process. Many of these points were conveyed in more than one venue and by more than one person or group.

Scientists and Others Favoring GOF Research

A variety of influenza and coronavirus researchers who conduct GOF research, and other life sciences researchers have stated that GOF studies are widely used and fundamental for understanding viruses, and therefore are crucial to undertake. This group generally favors conducting such research because it aims to benefit society. In their view, such research can be safely conducted under current oversight frameworks and further restrictions will impede valuable work that will lead to important scientific information about these viruses, leading to better drugs and vaccines, as well as to improving the specificity of surveillance, particularly for influenza. In addition, some GOF studies are viewed as essential, specifically those that alter host range or enhance pathogenicity in order to develop animal models of disease (for example, with SARS-CoV) or GOF studies that generate drug or countermeasure resistance, which are important in satisfying various FDA requirements for marketing approval. Those who support GOF studies also point out that such studies are needed for predicting what amino acid changes are important for human transmission and therefore are important for the selection of candidate vaccine viruses. They also argue that GOF studies are important for prioritizing viruses for risk management (surveillance) and that further work will make these applications more robust. These

[74] *Risk and Benefit Analysis of Gain-of-Function Research, Final Report*. Gryphon Scientific, April 2016. http://www.gryphonscientific.com/wp-content/uploads/2016/04/Risk-and-Benefit-Analysis-of-Gain-of-Function-Research-Final-Report.pdf

individuals also pointed to the risks associated with not doing GOF research (generally due to a lack of preparedness for natural public health threats) and argued that they must also be considered.

While acknowledging there are risks associated with GOF research, proponents believe those risks are manageable and have been overstated by some, as evidenced by the fact that laboratory acquired infections are rare and infections in the community as a result of releases from a laboratory are almost unknown. While risk cannot be zero, the work can be conducted safely and securely with appropriate risk mitigation including containment along with good training and with the implementation of robust occupational medicine programs. Alternatives to GOF do not always provide the full answer to key questions and may yield misinformation. Supporters of GOF studies have also expressed concerns about the effects of the current funding pause and possible additional oversight on the field of virology and young researchers, and feel that there are costs of not undertaking the work in question. A major need is for better definition of what is meant by GOF with a clear distinction between GOF studies and GOF studies of concern. Some have suggested that only viruses with increased transmissibility and pathogenicity represent risks that exceed those of other infectious diseases research. They have also noted that SARS and MERS viruses are different from influenza, and require a different risk assessment approach since they are already virulent human pathogens; GOF research is needed to develop animal models that will benefit development of countermeasures for coronaviruses. Some supporters have acknowledged that there may be some experiments that should not be done. Finally, proponents of GOF research have stated that the risks from naturally occurring influenza viruses, which they argue could be reduced through GOF work, are greater than risks from performing GOF studies.

Scientists and Others Critical of GOF Studies

Opponents and critics of GOF research have generally focused their concern on a subset of GOF studies—those that involve enhancing the pathogenicity and/or transmissibility in mammals (particularly by the respiratory route), which may result in the generation of novel pathogens with pandemic potential. Critics have argued that the generation of novel laboratory pathogens with pandemic potential poses major public health risks and some have argued such studies should not be conducted. They have presented and published calculations that suggest a high probability of global outbreaks of influenza that might kill hundreds of millions of people, as a result of the release from a laboratory of a novel GOF virus. There is some disagreement about these estimates and how likely a pandemic might be, but opponents generally argue that even a relatively low probability of a potentially massive outbreak with major consequences is unacceptable. Some critics of GOF studies have acknowledged that there are a number of GOF studies that can and should be conducted.

Opponents of certain GOF studies have also argued that the benefits of GOF studies have been overstated, or are questionable, and that the benefits generally do not outweigh the biosafety risks. They also question claims about the effectiveness of risk mitigation strategies, since human factors and human error are unavoidable and hard to control, and institutional compliance and competence may vary. Critics have disputed the value of GOF studies to surveillance stating that it is not possible to predict phenotype from genotype; therefore predicting the pandemic risk of newly emergent strains is

not achievable given the current state of knowledge. Also, in their view, controlling outbreaks doesn't require GOF research.

Opponents of GOF research tend to favor alternative types of research that, in their view, can provide the same public health benefits without the large risks. It was suggested that the approach should be on reducing the risk by reducing the hazard, as opposed to focusing on mitigation of the risk. For example, if a universal influenza vaccine was developed, the need for many GOF experiments would be eliminated. Critics want to see funds currently used for GOF work provided to other types of research, which would be a better use of scarce resources in their view. Overall, they view preventing major public health problems as paramount, and see a need to define a critical set of experiments that should not be done, or only be done with additional strong oversight. Opponents are also concerned about proliferation and other factors that may lead to misuse and biosecurity threats. Finally, opponents have pointed out a moral issue if risks and benefits of certain GOF studies are not fairly distributed globally.

Funding Agencies

Public and private funding agencies support GOF research that has raised concerns with the goal of improving public health and well-being. These organizations in the US and abroad are aware of the issues surrounding DURC/GOF studies and are working diligently to implement and comply with existing policies in their countries. Most funders have requirements and procedures in place as they apply policies and guidance to evaluate proposed work and to oversee funded work. Current approaches involve education and awareness campaigns, project risk evaluation, ethics reviews, development of risk mitigation plans, and post-award monitoring. Funders believe they can contribute to the GOF deliberative process as a result of their practical, on-the-ground experience with DURC and GOF. They are concerned that interpreting policy can be very challenging, since it requires considerable expertise and judgment. They would welcome workable policies with clear guidance and have noted some unintended consequences of the funding pause, which affected some GOF projects that had not raised particular concerns. Some foreign government funders view government funding as a poor control mechanisms because this does not cover privately funded research and research funded by other entities. National legislation, regulations, compliance, training, awareness-raising, and self-monitoring have been noted as important.

Biosecurity Experts and Others Concerned about National Security

The ultimate goal of national security professionals, as it pertains to life sciences research, is to protect public health from natural or man-made health threats. Those concerned with national security aim to prevent terrorists and others with malicious intent or misguided motives from using products or information from GOF research to cause harm. This may include deliberate release of pathogens into the community, targeting of researchers or research facilities, or interference with on-going research activities. GOF research represents biosecurity risks in addition to biosafety risks; these overlap but are different with regard to important legal, policy and regulatory issues. Managing biosafety risks may or may not also manage biosecurity risks; GOF policy must take both types of risk into account.

When trying to assess biosecurity threats, security professionals have noted the importance of avoiding assumptions and predictions about the motives and capabilities of those who might be planning biosecurity actions. Those in the security field gather a large variety of data, but often their information is imprecise and may require consideration of what is feasible and plausible. Because of the paucity of biosecurity events, it is very difficult to evaluate and predict the likelihood and consequences of a deliberate release or determine how to prevent and/or mitigate one, and different experts view this issue very differently. It was stated that research policy in itself is not be the appropriate solution to prevent specific biological threats but specific research policies could help raise awareness of security issues among researchers, which would be important.

Security and intelligence professionals have described the challenges associated with using classification as a potential risk mitigation strategy. Classification would effectively restrict access to sensitive research information and research products and would limit the number of laboratories able to perform the studies. This could be described as both a strength and a limitation, depending on one's perspective. Life sciences research that requires classification is typically classified at the outset; the retroactive classification of research that had been conducted in an open, academic setting is exceedingly difficult.

Scientific and Medical Journals

Scientific and medical journals have been at the forefront of the GOF issue. While a number of journals and families of journals have procedures in place for identifying DURC, including GOF and other biosecurity concerns in submitted manuscripts, many journal editors are not entirely comfortable with their role. Their mission is to transmit scientific information, not control it, and they may not have the security expertise or the access to such expertise to make the necessary judgments and decisions about risks associated with communicating certain research findings. Rejection and redaction are the major tools journals have to control dissemination of dual use information, and neither may actually address the concerns; they are also impractical to implement effectively. One suggestion voiced was to require that a description of the steps that were taken during conduct of the research to ensure safety be included in all manuscripts. Some journal editors and staff expressed a desire to get help in evaluating risks and mitigation strategies from an independent national group such as the NSABB and to involve them earlier in the overall process. Most think the publication stage is not the best point to exercise control or prevent misuse of data from GOF studies but realize they are the final gatekeepers. Earlier identification of DURC/GOF along with risk mitigation earlier in the research life cycle would reduce the burden on them. Also, new technology and novel publication venues make controlling information increasingly difficult, and, as noted above, not all journals are able to or choose to impose a rigorous review of manuscripts.

Countermeasure Developers

Companies and others that are attempting to develop vaccines and drugs against pathogens were represented in several discussions. Medical countermeasure (MCM) developers expressed quite divergent views and opinions. Those favoring GOF research argued that such work is absolutely

necessary for antiviral drug development because GOF experiments to select for drug resistant mutants as well as to develop animal models are part of the critical path to marketing approval. In their view, GOF studies also have had a major influence on developing influenza vaccines, both seasonal and pandemic, and are likely to result in improved ways to make even better vaccines in the future. GOF experiments are required for selection of strains with better growth properties, with key mutations that alter important phenotypes needed in the vaccine strain, and with incorporating characteristics of strains that are likely to emerge into proven backbones. It was noted that GOF studies that enhance virulence can help inform vaccine designers about which mutations to avoid incorporating into vaccine strains. This group is concerned that their efforts to improve public health may be limited or impeded by new policies and urge careful consideration of their needs as decisions are made.

Conversely, other MCM developers expressed the view that vaccine production now is little dependent on GOF research and that any possible benefits will be far into the future, although some feel long-term potential is there. Those who criticize GOF studies on these grounds have argued that vaccines are developed in response to strains that emerge as threats, rather than preemptively based on strains that might be predicted as threats. Rather than supporting GOF studies to enhance vaccine production and drug development, it has been suggested that the other constraints that impede MCM development be addressed, such as streamlining FDA approval procedures and improving manufacturing processes, which would have a much greater impact. These critics suggest limiting current GOF-related efforts and focusing attention and resources in other directions. Overall, they believe that impact of GOF research on vaccine and drug development has been overstated, and that the benefits articulated are more theoretical than practical.

The General Public and Organizations Representing their Views.

A number of stakeholders stressed the importance of having meaningful public engagement with input and participation as part of the deliberative process. It is important that communities that might be affected by accidents or the misuse of research have a say in the research that is being conducted, however, but this may not generally be the case in their view. Real transparency, with the public good as the foremost consideration, must be part of a truly independent decision-making process. They note that it is important to maintain public trust in the scientific enterprise by involving non-scientists at stages when their views can still have an impact on policy-making. Public opinion of science is harmed when decisions that influence public health and safety are made without such input or the input has no real impact. Conversely, effective community engagement can convert sceptics to supporters. More than one participant raised the concern that if risks and benefits are not equitably distributed, it is a serious ethical issue[75].

Other issues that were mentioned include: how harms will be compensated if a laboratory incident were to affect the surrounding community; the need for enough resources to conduct research safely; and the opportunity to learn from other industries such as the nuclear industry.

[75] The ethical issues are discussed in more depth elsewhere, notably, Dr. Michael Selgelid's ethical analysis and the section of this report on Ethical Values and Decision-Making Frameworks.

Research Institutions

Representatives of universities and other research institutions generally noted that there is already significant oversight of DURC and GOF at both the Federal and institutional levels. Biosafety professionals noted that potentially high risk projects would receive thorough scientific review and risk assessment, resulting in the development of risk mitigation plans, and on-going monitoring as a result of policies and requirements that are already in place. They cited concerns over any increase in compliance that would impose burdens on their already limited resources or impede researchers from doing valuable work. They have difficulty, at times, deciding what is DURC when reviewing specific projects and would welcome more specificity and guidance. Many emphasized the need for policies that are unambiguous and straightforward to implement.

Public Health Officials

Public health officials have expressed diverse opinions. Some believe that GOF research has and can continue to improve surveillance efforts, as well as vaccine and therapeutic development. Others expressed concerns that an accident involving a laboratory pathogen for which there are no countermeasures would be very concerning and difficult to respond to. At the local level it is important to have public health involvement in the decision-making process because they will be incident responders. Strong connections with state and local laboratories should be established for sharing information and might include involving them in the review process. It was also noted that GOF and related policies may impact sample sharing and impede international relations relating to public health efforts.

International Perspectives

A number of participants noted that there is much interest in the GOF/DURC issue internationally, and the international community is looking to see what the USG will do as a result of the deliberative process. It was noted that U.S. policy often influences policies globally and the international ramifications should be considered. Recent biosafety incidents in U.S. Federal labs have raised concerns among many in other countries about the ability of the U.S. to adequately manage risks. A number of countries have well-developed systems of policy and regulation that would address many or some GOF and DURC issues, though international policy approaches are generally somewhat different from those in the U.S. International experiences, activities, and perspectives were cited as important to consider in the deliberative process. A collaborative approach and active attempts to engage the international community was viewed as the most effective way to benefit all. Many favored launching an international dialogue soon, with development of broad concepts and points of agreement that could be shared by all, while still respecting national differences. In addition, it was suggested that academies of science and multi-national organizations such as the World Health Organization can play an important role in such interactions at the right time. Those with a particular interest in the international aspects of GOF research also cited ethical issues associated with the unequal distribution of risks and benefits

across rich and poor countries. It was noted that the European Commission uses a comprehensive ethics process for screening and monitoring DURC/GOF in research projects.[76]

Those with an Interest in the Deliberative Process Itself

A broad group of individuals offered comments on the deliberative process itself. This included: federal government personnel, ethicists, decision-making experts, policy experts, other scientists, and includes people who are also members of the previously-mentioned groups. Those concerned with the deliberative process generally called for a well-planned and executed, thorough, scientifically rigorous, and impartial RBA that is technically sound and socially acceptable. They favored a democratic deliberative process and a policy that incorporates decisions made by neutral parties. Policy should be created using risk-based and value-based approaches to achieve desired outcomes. They want the final policy resulting from the deliberative process to be capable of reasonably identifying and mitigating risks related to GOF while protecting scientific autonomy, research progress, discovery and innovation, public health, national security, and other critical interests.

Many see an adaptive process as desirable, and recommend collecting appropriate data about laboratory accidents and mitigation effectiveness. It was noted that risks and benefits will change as science advances. The funding decision-making process should be accountable and limit inherent conflicts of interest; the individuals or entities that make decisions is critical. Most favor using existing policies as the basis of policy for GOF, while acknowledging that current frameworks are not entirely adequate. The question of how to incorporate non-USG funded research into an acceptable framework was raised several times. Deciding how to decide is a key point.

Both proponents and critics of GOF studies criticized the term "gain-of-function" as being too broad and not descriptive enough. There was much discussion about the appropriate definition of GOF research of concern; many strong, often conflicting, views were expressed. Unfortunately, while it is important to have a working definition and criteria for what is GOF of concern as opposed to GOF, a binary distinction needed for deciding what requires extra scrutiny, GOF experiments are actually a continuum of increasing risk.

The funding pause was criticized for being too broad, and some described it as disruptive to scientific process. Finally, some feel that a definitive quantitative risk assessment is not possible because of the very large uncertainties and lack of critical information associated with doing such studies, and they question the value of any studies that are done.

[76] The EU Framework Programme for Research and Innovation, Horizon 2020. Guidance - *How to complete your ethics self-assessment*, version 1.0, 11 July 2014. http://ec.europa.eu/research/participants/data/ref/h2020/call_ptef/pt/h2020-call-pt-ria-ia_en.pdf#page=27

Appendix E. Consultations, Comments, and Sources Considered During NSABB Deliberations

Table 1A. Invited speakers, presenters, and panelists. This table lists invited individuals who presented at NSABB, NSABB working group, and the National Academies meetings. Members of the NSABB or an NSABB working group are listed if they presented as a subject matter expert on a specific topic.

Speaker/Commenter	Affiliation/Location	Venue
Regine Aalders, M.Sc.	Embassy of the Netherlands, Washington, D.C.	NSABB Full Board Meeting (January 7-8, 2016)
Nisreen AL-Hmoud, Ph.D, M.Phil.	Royal Scientific Society of Jordan	National Academies Workshop (March 10-11, 2016)
Ronald Atlas, Ph.D.	University of Louisville	National Academies Workshop (December 15, 2014)
Ralph Baric, Ph.D.	University of North Carolina at Chapel Hill	National Academies Workshop (December 15, 2014)
Kavita Berger, Ph.D.	Gryphon Scientific	NSABB Full Board Meeting (September 28, 2015), In-person WG Meeting (November 9, 2015)
Thomas Briese, Ph.D.	Columbia University	National Academies Workshop (December 15, 2014)
Michael Callahan, M.D., D.T.M.&H., M.S.P.H.	Massachusetts General Hospital; Harvard Medical School	National Academies Workshop (March 10-11, 2016)
Arturo Casadevall, M.D., Ph.D.	Johns Hopkins Bloomberg School of Public Health; mBio	NSABB Full Board Meeting (October 22, 2014), In-person WG Meeting (July 23, 2015)
Rocco Casagrande, Ph.D.	Gryphon Scientific	NSABB Full Board Meetings (September 28, 2015 and January 7-8, 2016), In-person WG Meeting (November 9, 2015), National Academies Workshop (March 10-11, 2016)
R. Alta Charo, J.D.	University of Wisconsin–Madison	National Academies Workshop (December 15, 2014), NSABB Full Board Meeting (January 7-8, 2016)
Susan Coller-Monarez, Ph.D.	U.S. Department of Homeland Security	In-person WG Meeting (July 23, 2015)
Louis (Tony) Cox, Ph.D., S.M.	Cox Associates	National Academies Workshop (March 10-11, 2016)
Mark Denison, M.D.	Vanderbilt University	National Academies Workshop (December 15, 2014), NSABB Full Board Meeting (January 7-8, 2016)
Dennis Dixon, Ph.D.	U.S. National Institutes of Health	NSABB Full Board Meeting (November 25, 2014)
Marianne Donker, Ph.D.	Ministry of Health, Welfare and Sport, Netherlands	In-person WG Meeting (July 23, 2015)
Philip Dormitzer, M.D., Ph.D.	Novartis Vaccines	National Academies Workshop (December 15, 2014)
Ruxandra Draghia-Akli, M.D., Ph.D.	European Commission	In-person WG Meeting (July 23, 2015), National Academies Workshop (March 10-11, 2016)
Rebecca Dresser, J.D.	Washington University in St. Louis	NSABB Full Board Meeting (September 28, 2015)
Paul Duprex, Ph.D.	Boston University, NEIDL Institute	NSABB Full Board Meeting (October 22, 2015)
Gerald Epstein, Ph.D.	White House Office of Science and Technology Policy	In-person WG Meeting (July 23, 2015)

Stephen Eubank, Ph.D.	Virginia Polytechnic Institute and State University	NSABB Full Board Meetings (October 22, 2014 and January 7-8, 2016)
Scott Ferson, Ph.D.	Applied Biomathematics	NSABB Full Board Meeting (October 22, 2014)
David Fidler, J.D., M.Phil.	Indiana University, Bloomington	NSABB Full Board Meeting (January 7-8, 2016)
Harvey Fineberg M.D, Ph.D.	University of California, San Francisco	National Academies Workshops (December 15, 2014 and March 10-11, 2016)
Adam Finkel, Sc.D., M.P.P.	University of Pennsylvania Law School	National Academies Workshops (March 10-11, 2016)
Baruch Fischhoff, Ph.D.	Carnegie Mellon University	NSABB Full Board Meeting (October 22, 2014), National Academies Workshop (December 15, 2014)
Robert Fisher, Ph.D.	U.S. Food and Drug Administration	National Academies Workshop (March 10-11, 2016)
Ron Fouchier, Ph.D.	Erasmus Medical Center	National Academies Workshop (December 15, 2014), NSABB Full Board Meeting (January 7-8, 2016)
David Franz, D.V.M., Ph.D.	Former Commander, United States Army Medical Research Institute for Infectious Diseases	In-person WG Meeting (July 23, 2015)
Christophe Fraser, Ph.D.	Imperial College	National Academies Workshop (December 15, 2014)
Richard Frothingham	Duke University	National Academies Workshop (March 10-11, 2016)
Keiji Fukuda, M.D., M.P.H.	World Health Organization	National Academies Workshop (March 10-11, 2016)
George F. Gao, D.V.M., D.Phil.	Chinese Academy of Sciences; Chinese Center for Disease Control and Prevention	National Academies Workshop (March 10-11, 2016)
Gigi Kwik Gronvall, Ph.D.	University of Pittsburgh Medical Center, Center for Health Security	National Academies Workshop (December 15, 2014), NSABB Full Board Meeting (January 7-8, 2016)
Charles Haas, Ph.D.	Drexel University	National Academies Workshop (December 15, 2014)
Andrew M. Hebbeler, Ph.D.	U.S. Department of State	NSABB Full Board Meeting (October 22, 2014), National Academies Workshop (December 15, 2014)
Ruthanne Huising, Ph.D., M.Sc.	McGill University	National Academies Workshop (March 10-11, 2016)
Gavin Huntley-Fenner, Ph.D.	Huntley-Fenner Advisors	National Academies Workshops (December 15, 2014 and March 10-11, 2016)
Jo Husbands, Ph.D.	Board on Life Sciences of the U.S. National Academies of Sciences, Engineering and Medicine	In-person WG Meeting (July 23, 2015), NSABB Full Board Meeting (January 7-8, 2016)
Michael Imperiale, Ph.D.	University of Michigan	National Academies Workshop (December 15, 2014), NSABB Full Board Meeting (January 7-8, 2016)
Thomas Inglesby, M.D.	University of Pittsburgh Medical Center, Center for Health Security	NSABB Full Board Meeting (October 22, 2014 and January 7-8, 2016)
Barbara Jasny, Ph.D.	Science	In-person WG Meeting (July 23, 2015), NSABB Full Board Meeting (January 7-8, 2016)
Daniel Jernigan, M.D., M.P.H.	U.S. Centers for Disease Control and Prevention	NSABB Full Board Meeting (January 7-8, 2016)
Barbara Johnson, Ph.D., R.B.P.	Biosafety Biosecurity International	National Academies Workshop (December 15, 2014)
John Kadvany, Ph.D.	Independent consultant on decision science	Full Board Meeting (January 7-8, 2016)
Joseph Kanabrocki, Ph.D., C.B.S.P.	University of Chicago	In-person WG Meeting (January 22, 2015), In-person WG Meeting (July 23, 2015)

Isidoros Karatzas, Ph.D.	European Commission	WG Meeting (February 16, 2016)
Yoshihiro Kawaoka, D.V.M., Ph.D.	University of Wisconsin, Madison	NSABB Full Board Meetings (October 22, 2014 and January 7-8, 2016), National Academies Workshop (December 15, 2014)
George Kemble, Ph.D.	3-V Biosciences	National Academies Workshop (December 15, 2014)
Lawrence Kerr, Ph.D.	U.S. Department of Health and Human Services	WG Meeting (November 5, 2015), National Academies Workshop (March 10-11, 2016)
Gregory Koblentz, Ph.D., M.P.P.	George Mason University	National Academies Workshop (December 15, 2014)
Todd Kuiken, Ph.D.	The Woodrow Wilson Center	In-person Meeting (July 23, 2015)
Robert Lamb, Ph.D., Sc.D.	Northwestern University; Howard Hughes Medical Institute	National Academies Workshop (December 15, 2014)
Linda Lambert, Ph.D.	U.S. National Institutes of Health	In-person WG Meeting (July 23, 2015)
Gabriel Leung, M.D., M.P.H.	University of Hong Kong	National Academies Workshop (March 10-11, 2016)
Carol Linden, Ph.D.	U.S. Biomedical Advanced Research and Development Authority	National Academies Workshop (December 15, 2014)
W. Ian Lipkin, M.D.	Columbia University	NSABB Full Board Meeting (October 22, 2014)
Marc Lipsitch, Ph.D.	Harvard School of Public Health	NSABB Full Board Meetings (October 22, 2014 and January 7-8, 2016), National Academies Workshop (December 15, 2014)
Patricia Long, J.D., LL.M.	U.S. Department of Health and Human Services	In-person WG Meeting (July 24, 2015)
Nicole Lurie, M.D., M.S.P.H.	U.S. Department of Health and Human Services	NSABB Full Board Meeting (October 22, 2014); In-person WG Meeting (July 23, 2015)
Eric Meslin, Ph.D.	Indiana University School of Medicine	NSABB Full Board Meeting (September 28, 2015)
Corey Meyer, Ph.D.	Gryphon Scientific	NSABB Full Board Meeting (September 28, 2015), In-person WG Meeting (November 9, 2015)
Jonathan Moreno, Ph.D.	University of Pennsylvania	NSABB Full Board Meeting (January 7-8, 2016), National Academies Workshop (March 10-11, 2016)
Kara Morgan, Ph.D., M.S.E.S.	Battelle	National Academies Workshop (March 10-11, 2016)
Rebecca Moritz, M.S., C.B.S.P., S.M.(NRCM)	University of Wisconsin–Madison	National Academies Workshop (December 15, 2014)
Kalyani Narasimhan, Ph.D.	Nature Publishing Group	In-person WG Meeting (July 23, 2015)
Kimberly Orr, Ph.D.	U.S. Department of Commerce	In-person WG Meeting (July 23, 2015)
Michael Osterholm, Ph.D., M.P.H.	University of Minnesota	NSABB Full Board Meeting (October 22, 2015)
Kenneth Oye, Ph.D.	Massachusetts Institute of Technology	In-person WG Meeting (July 23, 2015)
Christopher Park	U.S. Department of State	In-person WG Meeting (July 23, 2015)
Jean Patterson, Ph.D.	Texas Biomedical Research institute	In-person WG Meeting (January 22, 2015)
Daniel Perez, Ph.D.	University of Maryland	NSABB Full Board Meeting (October 22, 2014)

Janet Peterson, C.B.S.P.	University of Maryland	NSABB Full Board Meeting (October 22, 2014)
Philip Potter, Ph.D.	St. Jude Children's Research Hospital	NSABB Full Board Meeting (January 7-8, 2016), National Academies Workshop (March 10-11, 2016)
David Relman, M.D.	Stanford University	National Academies Workshop (December 15, 2014), NSABB Full Board Meeting (January 7-8, 2016)
David B. Resnik, J.D., Ph.D.	U.S. National Institutes of Health	NSABB Full Board Meeting (October 22, 2014)
Colin Russell, Ph.D.	University of Cambridge	National Academies Workshop (December 15, 2014)
Monica Schoch-Spana, Ph.D.	University of Pittsburgh Medical Center, Center for Health Security	National Academies Workshops (December 15, 2014 and March 10-11, 2016)
Stacey Schultz-Cherry, Ph.D.	St. Jude Children's Research Hospital	NSABB Full Board Meeting (October 22, 2014), National Academies Workshop (December 15, 2014)
Michael Selgelid, Ph.D.	Monash University	NSABB Full Board Meetings (September 28, 2015 and January 7-8, 2016), National Academies Workshop (March 10-11, 2016)
Ethan Settembre, Ph.D.	Seqirus	National Academies Workshop (March 10-11, 2016)
Richard Sever, Ph.D.	Cold Spring Harbor Laboratories Press; bioRxiv	In-person WG Meeting (July 23, 2015)
Michael Shaw, Ph.D.	Centers for Disease Control and Prevention	In-person WG Meeting (July 23, 2015)
Bill Sheridan, M.B., B.S.	BioCryst Pharmaceuticals Inc.	NSABB Full Board Meeting (October 22, 2014)
Kanta Subbarao, M.B.B.S., M.P.H.	National Institutes of Health	National Academies Workshop (December 15, 2014), NSABB Full Board Meeting (January 7-8, 2016)
Jill Taylor, Ph.D.	Wadsworth Center, NYS Department of Public Health	NSABB Full Board Meeting (January 7-8, 2016)
Robert Temple, M.D.	Food and Drug Administration	In-person WG Meeting (July 23, 2015)
Volker ter Meulen, M.D., Ph.D.	European Academies Science Advisory Council	National Academies Workshop (March 10-11, 2016)
Eileen Thacker, D.V.M., Ph.D., D.A.C.V.M.	U.S. Department of Agriculture	In-person WG Meeting (July 23, 2015)
Silja Vöneky, Prof., Dr., jur.	University of Freiburg; German Ethics Council	National Academies Workshop (March 10-11, 2016)
Robert Webster, Ph.D.	St. Jude Children's Research Hospital	National Academies Workshop (December 15, 2014)
Jerry Weir, Ph.D.	U.S. Food and Drug Administration	National Academies Workshop (December 15, 2014)
Robbin Weyant, Ph.D., R.B.P. (ABSA)	U.S. Centers for Disease Control and Prevention	National Academies Workshop (December 15, 2014), In-person WG Meeting (July 23,2015)
Beth Willis	Co-founder, Frederick Citizens for Bio-lab Safety	NSABB Full Board Meeting (January 7-8, 2016)
Carrie Wolinetz, Ph.D.	U.S. National Institutes of Health	NSABB Full Board Meetings (May 5, 2015 and January 7-8, 2016)

Table 1B. Public Commenters. Individuals and organizations that provided written or oral public comments to the NSABB via email and/or at NSABB meetings.

Commenter	Affiliation/Location (if provided)
Regine Aalders, M.Sc.	Embassy of the Netherlands, Washington, D.C.
Richard S. Adams	
Ralph Baric, Ph.D.	University of North Carolina at Chapel Hill
RADM Kenneth W. Bernard, M.D.	U.S. Public Health Service (ret.)
Rocco Casagrande, Ph.D.	Gryphon Scientific
Rolan O. Clark	
Derrin Culp	White Plains, New York
Annie De Groot M.D.	EpiVax Inc.
Mark Denison, M.D.	Vanderbilt University
Nicholas Evans, Ph.D.	University of Pennsylvania
David S. Fedson, M.D.	Sergy Haut, France
Ron Fouchier, Ph.D.	Erasmus Medical Center
Gregory Frank, Ph.D.	Infectious Diseases Society of America
Matthew Frieman, Ph.D.	University of Maryland
Deborah Gold, M.P.H., C.I.H.	Pacifica, California
Peter Hale	Foundation for Vaccine Research
Elizabeth Hart	Adelaide, South Australia
Denise Hein	
Thomas Inglesby, M.D.	University of Pittsburgh
Tyler John	National Institutes of Health
Laura H. Kahn, M.D., M.P.H., M.P.P.	Woodrow Wilson School of Public and International Affairs, Princeton University
Andy Kilianski, Ph.D.	National Research Council Fellow at US Army
Lynn C. Klotz, Ph.D.	Center for Arms Control and Non-proliferation
Bill Kojola	Silver Spring, Maryland
F. Gerard Lelieveld	The Hague, Netherlands
Marc Lipsitch, Ph.D.	Harvard School of Public Health
Kim R. Loll	Frederick County & City Containment Laboratories Community Advisory Committee

Corey Meyer, Ph.D.	Gryphon Scientific
Carlos S. Moreno, Ph.D.	Emory University School of Medicine
Kara Morgan, Ph.D.	Battelle
Peter Murakami	Baltimore, Maryland
Daniel O'Connell	Albany, Oregon
Megan Palmer, Ph.D.	Center for International Security and Cooperation, Stanford University
Dustin Phillips	Louisville, Kentucky
Stanley Plotkin, M.D.	University of Pennsylvania
Ryan Ritterson	Gryphon Scientific
George Rudy	Frederick County & City Containment Laboratory Community Advisory Committee
Steven L. Salzberg, Ph.D.	Johns Hopkins University School of Medicine
Shannon Scott	
Billie Sellers	
Nariyoshi Shinomiya, M.D., Ph.D.	National Defense Medical College, Japan
Lone Simonsen, Ph.D.	George Washington University
Andrew Snyder-Beattie	Future of Humanity Institute, University of Oxford
Charles R. Stack, M.P.H.	University of Illinois at Chicago
Kanta Subbarao, M.B.B.S., M.P.H.	National Institutes of Health
John Steel, Ph.D.	Emory University
Kimball Ward	
Simon Warne, Ph.D.	UK Scientific Advisory Committee on Genetic Modification
Gary Whittaker, Ph.D.	Cornell University
Frances Williams, R.N., M.S.	Frederick Citizens for Bio-lab Safety
Beth Willis	Frederick Citizens for Bio-lab Safety
David Wolinsky	Fredrick, Maryland
American Association of Immunologists	American Association of Immunologists (AAI)
Infectious Diseases Society of America	Infectious Diseases Society of America (IDSA)

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http://ec.europa.eu/research/participants/data/ref/h2020/other/hi/guide_research-dual-use_en.pdf

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Appendix F. NSABB Framework for Guiding the Risk and Benefit Assessments

The National Science Advisory Board for Biosecurity developed the recommendations contained in the following section as part of its charge stemming from 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*. As part of its charge, the NSABB was to provide advice on the design, development, and conduct of risk and benefit assessments for gain-of-function studies. The *Framework for Guiding the Conduct of Risk and Benefit Assessments of Gain-of-Function Research* which follows fulfills this portion of the NSABB's charge and was developed with the aim of helping to generate risk and benefit assessments that would provide information that would allow the NSABB to make sound, evidence-based recommendations.

FRAMEWORK FOR CONDUCTING RISK AND BENEFIT ASSESSMENTS OF GAIN-OF-FUNCTION RESEARCH

RECOMMENDATIONS OF THE NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

National Science Advisory Board for Biosecurity
MAY 2015

TABLE OF CONTENTS

PREAMBLE

The National Science Advisory Board for Biosecurity developed the recommendations contained in this document as part of its charge stemming from 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*, issued on October 17, 2014. As part of its charge, the NSABB is to 1) provide advice on the design, development, and conduct of risk and benefit assessments for gain-of-function studies, and 2) provide formal recommendations on the conceptual approach to the evaluation of proposed gain-of-function studies. This document was unanimously approved by the committee on May 5, 2015 and fulfills the first portion of the NSABB's charge. The recommendations in this document will guide the National Institutes of Health as it commissions a formal assessment of the potential risks and benefits associated with gain-of-function research involving pathogens with pandemic potential. The results of the risk and benefit assessments will inform the NSABB as it develops its recommendations to the United States Government about how to evaluate such studies.

BACKGROUND AND INTRODUCTION

Most genetic manipulations of microorganisms do not raise significant safety or security concerns; these studies are routinely conducted for valid scientific purposes using non-pathogenic organisms or biologic systems and are subject to appropriate Federal and institutional oversight. However, safety and security concerns may arise when certain types of manipulations, which introduce stable genetic mutations, are employed to better understand some pathogens or toxins, sometimes enhancing the ability of those agents to harm their hosts.

Recently, the phrase "gain-of-function (GOF) research" has come to describe certain studies that increase the ability of a pathogen to cause disease. This phrase achieved prominence after two groups published findings demonstrating that highly pathogenic avian influenza H5N1 viruses with a small number of engineered mutations became transmissible between mammals by respiratory droplets.[77,78] Such studies were undertaken to help define the fundamental nature of human-pathogen interactions, with the goal of enabling assessment of the pandemic potential of emerging infectious agents, informing public health and preparedness efforts, and furthering medical countermeasure development. However, such GOF studies may entail biosafety and biosecurity risks, and significant concerns have been raised about whether these studies generate information that could be misused to cause harm or whether the modified viruses could pose a pandemic threat if they were to be accidentally or intentionally released.

In 2012, a voluntary suspension of certain GOF studies involving highly pathogenic avian influenza H5N1 viruses was undertaken by the influenza research community.[79] During that time, policymakers considered whether certain GOF studies should be conducted using Federal funds, and if so, how those studies could be safely conducted. The Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) issued new biosafety guidelines for working with highly pathogenic avian influenza strains.[80,81] The U.S. Department of Health and Human Services (HHS) developed a framework for guiding its funding decisions about projects that may generate highly pathogenic H5N1 viruses that are transmissible between mammals by respiratory droplets.[82] This funding framework was later expanded to include H7N9 influenza viruses as well.[83] Under this framework, HHS considers newly submitted research project proposals involving certain GOF studies for their scientific and public health merits as well as associated biosafety, biosecurity, and dual use risks. HHS also identifies appropriate risk mitigation measures that are required. Studies that are deemed acceptable for funding may then proceed in accordance with any agreed-upon risk mitigation measures.

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[77] Imai et al. Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. *Nature* 486, 21 June 2012

[78] Herfst et al. Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets. *Science* 336, 22 June 2012

[79] Fouchier et al. Pause on avian flu transmission studies. *Nature* 481, 26 January 2012.

[80] Gangadharan D, Smith J, and Weyant R. Biosafety Recommendations for Work with Influenza Viruses Containing a Hemagglutinin from the A/goose/Guangdong/1/96 Lineage, Morbidity and Mortality Weekly Report 62(RR06); 1-7. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6206a1.htm

[81] *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*. http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines

[82] *Framework for Guiding Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets*, February 21, 2013. http://www.phe.gov/s3/dualuse/Documents/funding-hpai-h5n1.pdf

[83] Jaffe, HW, Patterson, AP, and Lurie, N. Avian Flu: Extra Oversight for H7N9 Experiments. *Nature* 500, 07 August 2013. http://www.nature.com/nature/journal/v500/n7461/full/500151a.html

Given the biosafety incidents in U.S. Federal laboratories during the summer of 2014 and renewed concerns regarding laboratory safety and biosecurity, the U.S. government (USG) determined that the risks and benefits of GOF research must be re-evaluated.[84] A robust and broad deliberative process that will result in the adoption of a new Federal GOF research policy (which will apply to research funded by U.S. agencies whether conducted in the U.S. or abroad) has been undertaken. While this process takes place, the USG has instituted a pause in the provision of new USG funding for certain GOF research involving influenza, Middle East Respiratory Syndrome coronavirus (MERS) or Severe Acute Respiratory Syndrome coronavirus (SARS) viruses—pathogens determined to have pandemic potential. Restrictions on new funding apply as follows:

> *New USG funding will not be released for gain-of-function research projects that may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. This restriction would not apply to characterization or testing of naturally occurring influenza, MERS, and SARS viruses, unless the tests are reasonably anticipated to increase transmissibility and/or pathogenicity.*

In parallel, the USG has encouraged the research community (both those who receive USG funding and those who do not) to join in adopting a voluntary pause on any on-going research that involves the types of studies that are subject to the funding restriction above.

The deliberative process involves both the National Science Advisory Board for Biosecurity (NSABB) and the National Academies, and involves explicit evaluation of the possible risks and potential benefits of GOF research with potential pandemic pathogens. The NSABB serves as the official Federal advisory body for providing advice on oversight of this area of dual use research. The NSABB is providing the USG with specific recommendations regarding a conceptual approach to the evaluation of proposed GOF studies. The National Research Council and the Institute of Medicine of the National Academies are convening forums to engage the life sciences community as well as to solicit feedback from scientists and the public on optimal approaches to ensure effective Federal oversight of GOF research. These forums involve discussion of principles important for the design of risk and benefit assessments of GOF research and of NSABB draft recommendations.

The final NSABB recommendations and the discussions at the National Academies forums will be taken into consideration by the USG during the development and adoption of a new USG policy governing the funding and conduct of GOF research.

Thorough and scientifically rigorous risk and benefit assessments of GOF research involving pathogens with pandemic potential are needed to inform the deliberative process, and to provide the NSABB and the USG with objective and comprehensive information about the risks and benefits associated with certain types of GOF research. The USG has determined that an independent contractor will conduct the risk and benefit assessments (RA and BA). The contractor will provide personnel and expertise for conducting the RA and BA on certain GOF research involving pathogens with pandemic potential. The RA and BA are to be comprehensive, sound, and credible and must be able to withstand rigorous scrutiny by a variety of stakeholders. The contractor's analyses are to be guided by the overall guiding

[84] *U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS viruses*, October 17, 2014.

principles described herein. In planning and conducting the RA and BA, the contractor will take into account issues raised by recent biosafety incidents in USG laboratories.

While the funding pause and the RA and BA are limited to specific pathogens,[85] products of the RA and BA are intended to inform broader NSABB deliberations, which will involve recommendations on a conceptual approach to the evaluation of proposed GOF studies that may extend to other high-consequence pathogens. NSABB recommendations will inform the USG as it develops and adopts policies about whether certain types of GOF studies on high-consequence pathogens with pandemic potential should be supported and, if so, how such funding proposals should be evaluated.

A private contractor will conduct the RA and BA; however, the process is intended to be a cooperative effort involving participation by NIH and the NSABB, and informed by discussions held at the National Academies forums. The NIH Office of Science Policy is managing the overall deliberative process, providing the interface and facilitating the communications between the contractor and other entities, and overseeing the work by the contractor. The studies and resulting reports must comply fully with USG requirements, both procedurally and analytically, using existing guidance from Federal agencies and peer-reviewed sources and well-established methods. Concerns of other stakeholders, in addition to the USG, must be considered.

THE CHARGE TO THE NSABB

The NSABB has been charged with providing advice on the design, development, and conduct of risk and benefit assessments, and with providing recommendations to the USG on a conceptual approach to the evaluation of proposed GOF studies. In developing its recommendations, the NSABB will consider: the results of the RA and BA; the spectrum of potential risks and benefits associated with GOF studies; alternative methods that may be employed to yield similar scientific insights or benefits, while reducing potential risks; public discussions hosted by the National Academies; and any additional consultations with relevant subject matter experts, as needed, to ensure that all appropriate expertise is brought to bear on the issues. In advising on the design and conduct of the RA and BA, the NSABB will recommend assumptions to be included in the risk assessment; evaluate the scope and methodologies to be used in the risk assessment; consider the adequacy of the scenarios in the risk assessment and propose additional scenarios to address other concerns or factors, as appropriate; advise on the assessment of the benefits, including types of benefits that should be examined and methods for examining them; and provide advice at key milestones in the conduct of the RA and BA.

To satisfy this charge, the NSABB will convene, deliberate, and provide two deliverables to the USG:

- **Deliverable 1.** Advice on the design, development, and conduct of risk and benefit assessments.
- **Deliverable 2.** Formal recommendations on the conceptual approach to the evaluation of proposed GOF studies.

The framework outlined herein, and subsequent input provided by the NSABB at key milestones throughout the conduct of the RA and BA, are intended to satisfy Deliverable 1.

[85] *U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS viruses*, October 17, 2014.

THE NSABB'S PROCESS

In order to accomplish its charge regarding Deliverable 1, the NSABB established a Working Group (WG), composed of 13 NSABB members with a broad range of expertise including microbiology, biodefense, ethics, biosecurity, national security, biosafety, public health, and other relevant areas. The WG also included non-voting *ex officio* members from Federal agencies who contributed expertise in virology, national security, ethics, foreign policy, and other areas. The group convened during the period of December 2014 through April 2015 by telephone conference calls and held a one-day in-person meeting to discuss the design and conduct of the RA and BA and to begin to identify the information necessary to inform the Board's final recommendations to be issued in Deliverable 2. The discussions ranged broadly and included general concepts of overall importance as well as specific details that the contractor should consider and include as the RA and BA proceed. The WG's findings were consolidated into a series of recommendations that were discussed and developed further, and ultimately approved by the full Board on May 5, 2015. The recommendations in this Framework are intended to guide the NIH as it works with the contractor performing the RA and BA such that the assessments will be conducted in a way that will provide information that allows the NSABB to make sound, evidence-based recommendations. The NSABB acknowledged the strengths and limitations associated with such assessments, which primarily involve scientific and technical input, and has noted that other information, such as consideration of ethical, legal, and other viewpoints, should inform its final recommendations (Deliverable 2).

In guiding the design of the RA and BA, the NSABB focused on issues specific to GOF studies but noted that some other directly relevant studies are important for comparison and should be included in the assessments. Although the RA and BA focus on specific experiments and scenarios, the scope is intended to be sufficient to allow evaluation of the risks and benefits of not just single experiments, but also whole research programs to inform decisions pertaining to the entire USG research portfolio related to GOF studies with high consequence pathogens with pandemic potential.

Finally, an issue of central importance to the entire deliberative process is public trust in the scientific enterprise. A possible negative outcome associated with the GOF issue is the loss of public trust if a laboratory accident involving modified strains were to occur or if GOF research were intentionally misused to cause harm. Loss of public trust is a serious concern and its impact could be felt widely across the scientific community. The deliberative process should be conducted with an eye toward maintaining public trust in the scientific enterprise and oversight of scientific research. To help ensure public trust, and to ensure the NSABB's deliberations are informed by broad input and diverse perspectives, the NSABB seeks to maximize stakeholder input and public engagement during the deliberative process. Of note, the deliberative process includes public forums hosted by the National Academies that are intended to gather input and foster broad discussions by the scientific and other stakeholder communities. The first forum was held in December 2014;[86] a second will be held later in the process. Additionally, NSABB meetings are open to the public and the Board encourages attendees to provide comments, either verbally or in writing. The NSABB encourages comments and input at any time, which can be submitted by emailing NSABB@od.nih.gov.

[86] *Potential Risks and Benefits of Gain-of-Function Research: Summary of a Workshop*. National Research Council and the Institute of Medicine of the National Academies. The National Academies Press, Washington D.C., 2015. www.nap.edu.

RECOMMENDATIONS REGARDING THE DESIGN AND CONDUCT OF THE RA AND BA

Guiding Principles

Listed below (not necessarily in order of importance) are guiding principles that should underpin the risk and benefit assessments. These principles should inform and guide the contractor's efforts in performing the risk and benefit assessments.

1. There are potential risks and benefits associated with certain GOF life sciences research that should be formally and rigorously identified and analyzed. The possible risks and benefits of not doing this work also need to be thoroughly examined.

2. Alternative experimental approaches to GOF experiments that may provide the same or similar outcomes or additional/different benefits, without the same risks, should be identified and their relative risks, benefits, and limitations thoroughly and impartially analyzed. There may be different risks and benefits associated with these alternatives.

3. The RA and BA processes should start with a clear articulation of their purposes. The issues must be framed appropriately, with specific, relevant questions to be answered. The RA and BA should be conceptualized so as to provide information that is useful and informative for guiding NSABB recommendations about whether or not and how to pursue the types of scientific studies that are the subject of the assessments.

4. The scope of the RA and BA must be sufficiently comprehensive and delineated, with all aspects of the problem being clearly defined and considered at the outset. While the scope must be sufficiently detailed, it also must be appropriately narrowed to the particular subset of studies whose risks may be especially significant.

5. The concepts of clarity, transparency, consistency, and reasonableness must underpin the RA and BA. The processes must be well-documented and the final results and their interpretations should be clearly described and presented.

6. The assessments must be objective, scientifically rigorous, comprehensive, credible, and reasonable. Analyses of potential risks and benefits should be based on existing guidance, use real data to the extent possible, and employ established, tested, and peer-accepted methods. The RA and BA should include both qualitative and quantitative analyses to the extent feasible.

7. Analyses should examine the impact of risk mitigation strategies and practices, the effect of public health interventions, and whether countermeasures are effective against novel strains, as well as how these strategies are actually employed, which may involve human error, crisis conditions, or other factors that decrease their effectiveness.

8. The data used are critical to conducting the risk and benefit assessments. Sources of data, quality of data, assumptions made in analyses, limitations of data, and areas where more data are needed all require explicit documentation. However, insufficient or lack of quality data should not be grounds for not addressing issues pertinent to the goals of the assessments.

Particular consideration must be given to issues of uncertainty[87] and sensitivity[88] in presenting results. Ranges and bounds should be used to reflect the level of confidence in the results.

9. The RA should address what could go wrong as a result of conducting GOF research, and the probability and consequences of such events. The BA should address what beneficial outcomes might result from such research, how probable they are, the magnitude of their effects, and a realistic timeframe for realizing the benefits. Both risks and benefits may depend on other factors and have different timeframes. Any assumptions regarding factors that must be present for the risks or benefits to be realized should be explicitly identified.

10. The focus of the assessments should be on research studies conducted within the U.S. or supported by U.S. funding and conducted outside of the U.S., but should take into account the fact that laboratories throughout the world that are not funded by the U.S. government may also be conducting similar studies.

11. These principles largely apply to both the RA and BA; however, the benefits are not just reduction of the risks included in the risk assessment. It may not always be feasible to express risks and benefits in the same terms, but an effort should be made to do so when possible.

12. The RA must encompass a range of scenarios including "maximum reasonable foreseeable events" (i.e., worst case) as well as those with a range of probabilities. Low probability but high consequence events deserve particular attention. Both intentional (malevolent) and accidental events should be included in the analyses.

Pathogens and Pathogen Characteristics

Listed below are pathogens that are recommended for inclusion in the RA and BA to provide information about the risks and benefits associated with GOF research involving these specific agents; however, the NSABB's ultimate policy recommendations need not be limited to these specific pathogens. The risks and benefits analyzed in the assessments are intended to be representative of those associated with similar agents and experiments that may arise in the future. Most pandemics are associated with respiratory transmission, so agents in this category are of overarching concern. The NSABB considered adding a variety of agents, viral and bacterial, as well as agents having different transmission routes that might gain the property of respiratory transmission. The NSABB also discussed the pathogen characteristics that are most concerning.

[87] Uncertainty is the lack or incompleteness of information. Quantitative uncertainty analysis attempts to analyze and describe the degree to which a calculated value may differ from the true value; it sometimes uses probability distributions. Uncertainty depends on the quality, quantity, and relevance of data and on the reliability and relevance of models and assumptions used to fill data gaps. From *Science and Decisions: Advancing Risk Assessment*. National Research Council of the National Academies, The National Academies Press; Washington DC. 2009.

[88] Sensitivity is the degree to which the outputs of a quantitative assessment are affected by changes in selected input parameters or assumptions. From *Science and Decisions: Advancing Risk Assessment*. National Research Council of the National Academies, The National Academies Press; Washington DC. 2009.

Pathogens recommended for inclusion in the RA and BA:

1. **Influenza viruses.** Because of the significant differences among influenza strains, the NSABB recommends that three distinct strains be analyzed. These are:

    a. Seasonal influenza (e.g., currently circulating or historical H1N1, H3N2, and influenza B strains for which a significant portion of the general population has pre-existing immunity)
    b. Highly pathogenic avian influenza virus H5N1
    c. Low pathogenic avian influenza virus H7N9

2. **SARS-CoV**

3. **MERS-CoV**

Pathogen characteristics recommended for consideration in the RA and BA:

The RA and BA should include analysis of the risks and benefits associated with GOF experiments that are anticipated to increase the pandemic potential of pathogens. Toward this end, the following characteristics, which may be conferred to pathogens during the conduct of GOF studies, should be considered:

1. Enhanced pathogen production as a result of changes in the replication cycle or growth.

2. Enhanced morbidity and mortality in appropriate animal models.

3. Enhanced transmission in mammals (e.g., increased host or tissue range, altered route of transmission, infectivity above a certain threshold determined in an appropriate animal model).

4. Evasion of existing natural or induced immunity.

5. Resistance to drugs or evasion of other medical countermeasures such as vaccines, therapeutics, diagnostics.

Risk Categories

In order for the contractor to plan and conduct the risk assessment so that it will ultimately meet the needs of the NSABB, the scope of possible risks must be defined at the outset. The risk assessment should particularly examine any risks that are unique to GOF studies and examine the relative risks of GOF research compared to alternative approaches. It is important that all reasonable categories of risks be examined. Listed below are the categories of risks that the NSABB recommends be considered in the RA. There is some overlap between the categories, and of note, potential national biosecurity risks that should be considered are associated with most of the categories. For each of the risk categories, both intentional and accidental events that lead to risk should be considered, as appropriate. In addition, the analysis should consider the risks associated with certain GOF studies in the context of currently existing risks associated with the broader, national biomedical research portfolio and from the perspective of past experience. The RA should also consider the additive risks associated with conducting relevant GOF

studies at multiple locations. Where there are case studies or known examples of events that document various risks, these should be compiled and selected examples incorporated into the RA report.

1. **Biosafety:** Biosafety risks are those generally associated with laboratory accidents. Assessing these risks should include the magnitude of exposures, initial infections, transmission leading to secondary infections, and outbreaks in humans or animals. The issue of novel pathogenic strains for which we may be unprepared needs particular attention. The association of laboratory personnel with intermediary hosts should also be considered. The RA should evaluate the effect that public health interventions and occupational health and staff monitoring programs have on the risks posed by novel pathogens resulting from GOF studies, as compared to existing pathogens. The assessment should consider how the capabilities and containment features of the lab doing the work influence risk. The risks to lab workers and to the general public should be analyzed separately.

2. **Physical and personnel security (biosecurity):** Biosecurity risks are those associated with crime and terrorism involving pathogens resulting from GOF studies and would take into account the physical security of pathogens, risks associated with shipping and transporting pathogens, and the risk of illegitimate acts by "insiders," or laboratory employees. Biosecurity risks include physical breach, theft, loss or intentional release by lab personnel, malevolent acts, and terrorism. The RA should include consideration of the types of actors who would seek to misuse life sciences research information and materials as well as their capabilities to do so. The analysis should also consider specifically how the studies in question could be misused, whether terrorists might target labs to gain access to materials or scientific expertise, and include estimates of how great the threats may be.

3. **Proliferation:** The RA should consider how pursuing certain GOF studies may lead to expanded amounts of that research and, as a result, increased risk (biosafety, biosecurity, and others). Proliferation might occur if certain studies become standard or typical, or, conversely, if unpublished studies (due to safety or security concerns) are repeated, unwittingly by others. This analysis should take into account that biosafety standards vary in different countries and settings.

4. **Information risk:** Information risks are those associated with how the information generated by GOF studies, if made publically available, could enable others throughout the world to replicate such studies or generate pathogens for malevolent actions or threats to national security. Intellectual property threats may also be considered here.

5. **Agricultural:** This involves the risks to agriculturally-relevant animals such as pigs or chickens if a laboratory-modified pathogen produced during GOF studies was to be intentionally or accidentally released into populations of these animals. This also includes risks resulting from interaction between humans and other reservoir hosts.

6. **Economic risks:** Economic risks include monetary costs associated with releases of pathogens resulting from GOF studies, including loss of productivity, agricultural damage, liability, and the issue of accountability. Opportunity costs might also be considered.

7. **Loss of public confidence:** It is important to consider the possible loss of public trust in the scientific enterprise that might result if a laboratory accident involving modified pathogens were

to occur or if products or information from GOF research were intentionally misused to cause harm. Loss of public trust is a serious concern and its impact could be felt widely across the scientific community.

Benefit Categories

In order for the contractor to plan and conduct the BA so that it will ultimately meet the needs of the NSABB, the scope of potential benefits that may result from GOF research must be defined at the outset. The BA should particularly examine any unique benefits that could be realized as a result of GOF studies and examine the relative benefits of GOF research compared to alternative approaches. It is important that all reasonable categories of benefits be examined. Listed below are several categories of benefits that the NSABB recommends for inclusion in the BA. It should be noted that national security dimensions to the benefits associated with several categories should be considered. The NSABB notes that some benefits may only accrue if other associated events also take place. The NSABB also acknowledges the difficulty of analyzing some benefits, particularly those with long-term timeframes.

1. **Scientific knowledge**: These benefits include analysis of the types of scientific information that could be generated from GOF research, and an assessment of the value of such information for understanding the agents/diseases being studied (or other agents/diseases). The assessment should consider ways to quantify these benefits if possible. The BA should also analyze whether GOF research generates (or is likely to generate) unique scientific information that expands the knowledge base in ways that other research approaches cannot.

2. **Biosurveillance:** These benefits would include those relevant to the processes of gathering, integrating, analyzing, interpreting, and communicating essential information that might relate to disease activity and threats to human, animal, or plant health.[89] Specifically, the potential benefits of relevant GOF studies should be examined for benefits to:

    a. **Public Health Surveillance[90]:** How GOF research may contribute to efforts to improve public health by aiding detection and monitoring of pathogens in the real world, or help to better recognize or predict outbreaks in human populations, and inform decision-making.

    b. **Agricultural and domestic animal surveillance:** How GOF research may contribute to efforts to improve agricultural health by aiding detection and monitoring of pathogens in

[89] The National Association of County and City Health Officials, http://naccho.org/topics/emergency/biosurveillance/index.cfm, defines biosurveillance as a process of gathering, integrating, interpreting, and communicating essential information that might relate to disease activity and threats to human, animal, or plant health. For the public health professional, biosurveillance activities range from standard epidemiological practices to advanced technological systems, utilizing complex algorithms.

[90] The World Health Organization, http://www.who.int/topics/public_health_surveillance/en/, defines public health surveillance as the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice. Such surveillance can serve as an early warning system for impending public health emergencies; document the impact of an intervention, or track progress towards specified goals; and monitor and clarify the epidemiology of health problems, to allow priorities to be set and to inform public health policy and strategies. CDC defines public health surveillance as the ongoing, systematic collection, analysis, and interpretation of health data, essential to the planning, implementation and evaluation of public health practice, closely integrated with the dissemination of these data to those who need to know and linked to prevention and control. See http://www.cdc.gov/niosh/topics/flu/surveillance.html.

food-producing, domestic, or other animals so as to help to better recognize or predict outbreaks in such animals, and inform decision-making.

c. **Wildlife surveillance:** How GOF research may contribute to the improvement of surveillance in wildlife by aiding detection and monitoring of pathogens, or help to better recognize or predict outbreaks in such animals, and inform decision-making.

3. **Medical countermeasures:** For the following three benefits in particular, the benefit assessment should examine the relative benefits of GOF research compared to alternative approaches. The assessment should also consider whether, and if so, how, GOF research yields unique information that may not otherwise be possible.

   a. **Therapeutics**: How the research is likely to aid discovery and development of new or more effective therapeutics.

   b. **Vaccines:** How the research is likely to aid development and selection of new or more effective vaccines.

   c. **Diagnostics:** How the research is likely to aid development of new or better diagnostic methods and products.

4. **Informing policy decisions:** How information gained from GOF studies contributes, or is likely to contribute, to public health preparedness decisions such as informing countermeasure stockpiling decisions, guiding decisions about strain selection for vaccine development, or informing decisions about whether and how to mobilize resources or issue guidance in response to a newly emergent pathogen.

5. **Economic benefits:** Possible gains (monetary, employment, labor productivity, etc.) and cost savings associated with the results/outcomes of GOF studies, such as diminished health care costs due to vaccines or therapeutics, or other positive impacts on the economy.

Historical Perspectives from Analysis of Past Experiences

Naturally-occurring epidemics and pandemics can provide helpful background information that might inform the discussion about the risks associated with the infectious agents that are subjects of RA and BA. There is significant historical data on the mortality and morbidity associated with seasonal and pandemic influenza, as well as more recent data on the other pathogens recommended for inclusion the RA and BA studies. However, there are complexities and limitations to interpreting these data and trends that require further analysis. Valuable historical perspectives about past outbreaks of seasonal and pandemic influenza, SARS, and MERS viruses could be obtained by conducting quantitative analyses of global pathogen-associated morbidity and mortality. This information will supplement the RA and BA being undertaken as part of the deliberative process on GOF research, and will help inform the development of the NSABB's final recommendations (Deliverable 2).

Specifically, the NSABB recommends that an analysis be done for each pathogen, which summarizes existing data and information and, to the extent possible, includes:

1. Global morbidity and mortality data associated with seasonal influenza, pandemic influenza, SARS, and MERS, and trends in these data over time.

2. If applicable, comparison of the morbidity and mortality associated with seasonal and pandemic illness.

3. Historical information about the impact of illness on food production, particularly the swine and poultry industries.

4. Description of how the data utilized were collected, interpreted, and analyzed.

5. Qualitative review of the impact of vaccines and therapeutics on pathogen-associated morbidity and mortality.

Scenarios and Events to be Included in the RA

The RA should be based on a series of events that might occur during the course of conducting GOF research. It is anticipated that the contractor will develop a large list of possible events and scenarios that might be included. Because of time and resource constraints, only a subset will be analyzed in depth; however, it is important to define the total range of reasonably likely events so that the ones that are analyzed will be representative of the risks anticipated to be associated with GOF research more broadly. Scenarios should include analysis of the effects of risk mitigation approaches and include realistic examples where mitigation is effective and where it fails in some way. The analyses should incorporate examples that account for variability between labs and their practices.

Development and Selection of Events and Scenarios

Listed below are recommendations, derived from the Guiding Principles identified above, which should guide the contractor as specific scenarios are developed and proposed for analysis.

1. Scenarios and events should be scientifically, politically, and socially accurate and credible.

2. To the extent possible, events and scenarios should be realistic and based on actual examples, possibly including the recent laboratory accidents at Federal facilities.

3. The overall range of scenarios should encompass high and low risk events, high and low probability events, and maximum reasonably foreseeable (highly unlikely, but still credible) events.

4. The scenarios should involve events that are of concern to stakeholders, including the public, and include types that involve experimental manipulations that ultimately may be determined to be prohibited under any circumstances.

5. Scenarios involving security threats should be plausible but not necessarily based on specific, real-life examples, given that the security landscape is constantly evolving. Such scenarios should involve consideration of the prior actions or expressed intent of hostile groups, current and reasonably achievable technical capabilities of these groups, and how readily security threats could be achieved or enabled by a certain type of GOF study.

Categories of Events and Scenarios

Listed below are types of events and scenarios that the NSABB recommends for consideration in the RA. The contractor should propose more specific scenarios based on these categories.

1. Accidents due to equipment failure, human error, and system malfunction

2. Events that lead to direct infection of lab worker(s)

3. Accidental direct release into the environment, with possible exposure of the public

4. Scenarios that lead to secondary transmission of disease in the community, starting with an infected lab worker

5. Incidents that result from security failures, either building systems or personnel

6. Incidents stemming from inventory errors and those involved with laboratory transitions, such as laboratories relocating, principal investigators retiring, students graduating, etc.

7. Scenarios involving the escape of an infected animal

8. Scenarios that result in health and/or economic impacts on important animal species, particularly those important to the food supply

9. Insider threats: an internal breach of security (e.g., disgruntled lab worker, infiltration of a lab by an individual with nefarious intent)

10. External threats: an external breach of security (e.g., crime, targeting of a lab for theft of agents or materials)

11. Production of novel pathogens for malevolent acts or other illegitimate purposes based on information published about the results of GOF research

12. Natural disasters (e.g., earthquake, hurricane, tornado)

13. Accidents resulting from conduct of GOF research under sub-standard biosafety/biocontainment conditions or practices, either in the U.S. or internationally

14. Scenarios based on alternative experimental approaches to GOF research

Types of Experiments in RA

The scope of research that is of concern must be clearly defined at the outset. Not all research that involves genetic manipulations to alter a pathogen's phenotype should be examined in the RA and BA. Listed below are types of experiments recommended for consideration in the RA and BA, but the NSABB's ultimate policy recommendations need not be limited to the specific experiment types included in the assessments. The following list includes experiment types that should be incorporated into

scenarios to be modeled in the RA. Importantly, inclusion of these types of experiments is not intended to condemn or condone them. The goal is to get a broad sense of the risks and benefits associated with different experimental manipulations in the context of the pathogens identified above, recognizing that not all permutations of risks, agents, and scenarios can practically be analyzed in depth.

1. Passage in animals with the intent to alter host range and generate mammalian adapted strains or to develop an animal model of disease

2. Genetic modifications and/or selection for traits that may increase pathogenicity or transmissibility

3. Manipulations resulting in better growth or enhanced replication, for example, to make a vaccine strain

4. Selection for drug-resistant mutants

5. Antigenic escape studies, i.e., selecting for pathogens that are not neutralized by certain antibodies, such as those generated in response to a vaccine or monoclonal antibodies

6. Alternative experiments to GOF that may yield similar scientific information

Biosafety Assumptions for the RA

In order to assess the risks associated with GOF experiments it is necessary to define the biosafety level (BSL) and other related conditions under which the work may take place because differences in working conditions may significantly affect the risk of an experiment and possible adverse results. In the United States, the *Biosafety in Microbiological and Biomedical Laboratories* and the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*)[91] provide biosafety guidance regarding the conduct of risk assessments, and determination of appropriate laboratory practices and physical containment for research conducted with specific agents. These guidelines apply to certain Federally-funded research conducted in the U.S. and abroad and are frequently used by non-Federally-funded institutions and other countries as the model for biosafety guidance. The NSABB recommends that the contractor carefully examine current guidance for biocontainment, biosafety practices, training, and occupational health plans and incorporate these features into their analysis.

Different countries have varying biosafety standards, and not all individuals replicating GOF work (especially including those intending to misuse their materials or results) will necessarily abide by biosafety standards. Therefore, to examine the range of risks associated with conducting GOF studies under different biosafety conditions, the NSABB recommends that risks associated with GOF studies involving each pathogen be assessed both 1) under biosafety conditions that are recommended under current guidance for the relevant studies and 2) under a range of biosafety conditions, so that the effects of different levels of mitigation, or lack thereof, can be determined. Also, the NSABB recommends that the effects of adequate or inadequate occupational medicine/medical surveillance programs, training, standard operating procedures, and administrative controls be examined. This approach will provide information the NSABB needs to make recommendations about the conditions under which certain GOF studies might be performed to maximize safety and minimize unnecessary

[91] http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines

burden on the research. Finally, the NSABB recommends that the contractor investigate the status of biosafety guidance and biocontainment capabilities in other parts of the world, including guidance issued by the World Health Organization, and provide a summary of the findings.

Approaches and Methods for Assessing Risks and Benefits Associated with GOF Studies

The NSABB recommends that the following approaches be explored and employed by the contractor, as appropriate and reasonable, to assess the risks and benefits associated with relevant GOF studies. The contractor should examine these and other possible methods and identify those that might best be used to assess the specific categories of risks and benefits recommended above. Efforts to identify risks and benefits that are unique to GOF research should be emphasized.

1. Literature reviews and examination of knowledge indicators (e.g., science citation index), including consideration of quality and impact of information on the field.

2. Examination of commercialization indicators (e.g., number of patents), including considerations for quality and utility.

3. Interviews and consultations with a broad range of relevant experts about risks and benefits associated with GOF studies are highly recommended. Relevant experts might include those in various scientific disciplines, public health, clinical medicine, agriculture, private sector, global health, public policy, and national security, and should include experts both within and outside the United States. Consultations should include discussion of the important scientific questions remaining specifically for the pathogens being analyzed in the RA and BA and whether and how information from GOF studies may be utilized by relevant sectors. Discussions of how GOF studies contribute to research involving other pathogens with pandemic potential may also be useful. Interviews should also incorporate discussion of the perceived risks and benefits of alternatives to GOF studies.

4. Development of illustrative case studies or descriptions of instances where a GOF study has resulted in a specific risk or benefit.

5. Quantitative approaches to modeling the risks and benefits, particularly to public health. For instance, morbidity and mortality may be modeled for various scenarios of laboratory accidents, security breaches or intentional misuse, and/or public health responses. Additionally, if a GOF study were to accelerate vaccine or therapeutic production, it may be possible to model the positive effects on public health.

6. Quantitative approaches to modeling economic benefits and risks. For instance, if a GOF study would accelerate the development of a therapeutic or vaccine, the potential positive effects on jobs or productivity, as well as reduced health care costs in the event of a pandemic, might be estimated. In addition, the costs associated with an accidental release or malevolent act should be modeled.

7. Development of “event trees” illustrating processes leading to tangible events from GOF studies, employing expert elicitation to bound key events/nodes in processes.

Appendix G. NSABB Charter

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

CHARTER

NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

AUTHORITY

Authorized by 42 U.S.C. 217a, section 222 of the Public Health Service Act, as amended and Pub. L. 109–417, section 205 of the Pandemic and All-Hazards and Preparedness Act. The National Science Advisory Board for Biosecurity (NSABB) is governed by the provisions of the Federal Advisory Committee Act, as amended (5 U.S.C. app.), which sets forth standards for the formation and use of advisory committees.

OBJECTIVES AND SCOPE OF ACTIVITIES

The purpose of the NSABB is to provide, as requested, advice, guidance, and leadership regarding biosecurity oversight of dual use research, defined as biological research with legitimate scientific purpose that may be misused to pose a biologic threat to public health and/or national security. The NSABB will provide advice on and recommend specific strategies for the efficient and effective oversight of federally conducted or supported dual use biological research, taking into consideration both national security concerns and the needs of the research community to foster continued rapid progress in public health and agricultural research. Toward this end, the NSABB will also include providing strategies to raise awareness of dual use issues relevant to the life science and related interdisciplinary research communities.

DESCRIPTION OF DUTIES

The NSABB will be composed of subject matter experts who are not full-time employees of the Federal Government as well as ex officio members from Federal entities listed in the "Membership and Designation" section below, and will perform the following activities:

- Provide recommendations on the development of programs for outreach, education and training in dual use research issues for scientists, laboratory workers, students, and trainees in relevant disciplines.
- Advise on policies governing publication, public communication, and dissemination of dual use research methodologies and results.
- Recommend strategies for fostering international engagement on dual use biological research issues.

- Advise on the development, utilization and promotion of codes of conduct to interdisciplinary life scientists, and relevant professional groups.
- Advise on policies regarding the conduct, communication, and oversight of dual use research and research results, as requested.
- Advise on the Federal Select Agent Program, as requested.
- Address any other issues as directed by the Secretary of HHS.

AGENCY OR OFFICIAL TO WHOM THE COMMITTEE REPORTS

The NSABB will advise the Secretary of the Department of Health and Human Services (HHS), the Director of the National Institutes of Health (NIH), and the heads of all Federal entities that conduct, support or have an interest in life sciences research.

SUPPORT

Management and support services for the NSABB will be provided by the Office of Science Policy (OSP), within the Office of the Director, NIH. HHS and NIH staff will hold security clearances at the level of Secret or higher, as needed, to provide support to the NSABB.

ESTIMATED ANNUAL OPERATING COSTS AND STAFF YEARS

The estimated annual cost for operating the Committee, including compensation and travel expenses for members, but excluding staff support, is $274,900. The estimated annual person-years of staff support required is 1.5 at an estimated cost of $156,637.

DESIGNATED FEDERAL OFFICER

The Director, NIH, will assign a full-time or permanent part-time NIH employee to serve as the Designated Federal Officer (DFO) of the NSABB. In the event that the DFO cannot fulfill the assigned duties of the NSABB, one or more full-time or permanent part-time NIH employees will be assigned these duties on a temporary basis.

The DFO will approve or call all of the NSABB and subcommittee meetings, prepare and approve all meeting agendas, attend all Committee and subcommittee meetings, adjourn any meetings when it is determined to be in the public interest, and chair meetings when directed to do so by the Director, NIH, or the Director, OSP.

ESTIMATED NUMBER AND FREQUENCY OF MEETINGS

Meetings of the full committee will be held approximately two times within a fiscal year, and may be convened on an as-needed basis, at the call of the NSABB Executive Director or DFO. Meetings of the NSABB will be open to the public except as determined otherwise by the Secretary of Health and Human Services (Secretary), in accordance with subsection (c) of section 552b of Title 5 U.S.C. Notice of all meetings will be given to the public. In the event a portion of a meeting is closed to the public, as determined by the Secretary, in accordance with the Government in the Sunshine Act (5 U.S.C. 522b(c)) and the Federal Advisory Committee Act, a report will be prepared which will contain, as a minimum, a list of members and their business addresses, the Committee's functions, dates and places of meetings,

and a summary of the Committee's activities and recommendations made during the fiscal year. A copy of the report will be provided to the Department Committee Management Officer.

DURATION

Continuing.

TERMINATION

Unless renewed by appropriate action, the NSABB will terminate two years from the date this charter is filed.

MEMBERSHIP AND DESIGNATION

The NSABB will consist of not more than 25 voting members, including the Chair. Members will be appointed by the Secretary, HHS, in consultation with the heads of Federal departments and agencies that conduct or support life science research. The Secretary, HHS, will designate the Chair. All members will hold security clearances at the level of Secret or higher. Voting members are Special Government Employees and as such serve in their individual capacity as subject matter experts. None of these members serve as Representatives.

Areas of expertise to be represented on the NSABB, may include but are not be limited to:
Molecular Biology/Genomics
Microbiology (Bacteriology)
Microbiology (Virology)
Clinical Infectious Diseases/Diagnostics
Laboratory Biosafety and Biosecurity
Public Health/Epidemiology
Health Physicist/Radiation Safety
Pharmaceutical Production
Veterinary Medicine
Plant Health
Food Production
Bioethics
National Security
Military Biodefense Programs and Military Medicine
Intelligence
Biodefense
Law
Law Enforcement
Academia
Scientific Publishing
Industry Perspective
NIH Recombinant DNA Advisory Committee Experience/Perspective
Public Perspective
IBC perspective
Export Controls

There may be non-voting ex officio members from each of the following Federal entities:

- Executive Office of the President
- Department of Health and Human Services
- Department of Energy
- Department of Homeland Security
- Department of Veterans Affairs
- Department of Defense
- Department of the Interior
- Environmental Protection Agency
- Department of Agriculture
- National Science Foundation
- Department of Justice
- Department of State
- Department of Commerce
- Intelligence Community
- National Aeronautics and Space Administration
- Others as appropriate

Voting members will be invited to serve for overlapping terms of up to four years; terms of more than two years are contingent upon the renewal of the NSABB's Charter by appropriate action prior to its expiration. A voting member's term may be extended until a successor has been appointed.

A quorum for the NSABB and each of its subcommittees will consist of a majority of the appointed members eligible to vote. The nonvoting agency representatives will not be counted in calculating a quorum. Of the voting members, any who are recused from participating in an action on a particular issue, (e.g., due to a conflict of interest), will not be counted in calculating the quorum. All votes relating to any review of a recommendation by the NSABB will be open to the public unless the meeting has been closed to the public in accordance with the Government in the Sunshine Act and the Federal Advisory Committee Act.

SUBCOMMITTEES

As necessary, subcommittees and ad hoc working groups may be established by the NSABB Executive Director or DFO to perform functions within the Committee's jurisdiction. The advice/recommendations of the subcommittee/working group must be deliberated by the parent advisory committee. A subcommittee may not report directly to a Federal official unless there is statutory authority to do so.

Subcommittee membership may be drawn in whole or in part from the parent advisory committee. All subcommittee members may vote on subcommittee actions and all subcommittee members count towards the quorum for a subcommittee meeting. Ad hoc consultants do not count towards the quorum and may not vote. The Department Committee Management Officer will be notified upon establishment of each standing subcommittee and will be provided information on its name, membership, function, and estimated frequency of meetings.

RECORDKEEPING

Meetings of the Committee and its subcommittees will be conducted according to the Federal Advisory Committee Act, other applicable laws and Department policies. Committee and subcommittee records will be handled in accordance with General Records Schedule 6.2, Federal Advisory Committee Records, or other approved agency records disposition schedule. These records will be available for public inspection and copying, subject to the Freedom of Information Act, 5 U.S.C. 552.

FILING DATE

April 7, 2016

APPROVED

MAR 1 5 2016
Date

Sylvia M. Burwell

Appendix H. NSABB Roster

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