Working Paper Prepared by the NSABB Working Group on Evaluating the Risks and Benefits of Gain-of-Function Studies to Formulate Policy Recommendations

December 23, 2015

Preface

This working paper was developed by the NSABB working group tasked with evaluating the risks and benefits associated with gain-of-function studies and developing draft recommendations on a conceptual approach for the evaluation of proposed gain-of-function studies. This document is pre-decisional and intended as a deliberative document to be discussed at the meeting of the full NSABB on January 7 & 8, 2016. This is document is not a formal NSABB work product and should not be considered to be official NSABB findings or recommendations to the U.S. government. This document does not represent official policy of the U.S. government.

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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 policies are in place to help ensure that pathogen research is conducted safely and in ways to minimize the risks of laboratory accidents and security risks. Recently, and in the wake of a number of biosafety incidents at Federal facilities, concerns have been raised about certain "gain-of-function" (GOF) studies with the potential to generate pathogens with enhanced pathogenicity or transmissibility in mammals. The concerns center around whether a pathogen with enhanced characteristics could be accidentally or intentionally released from a laboratory, potentially exposing surrounding populations to a pathogen with pandemic potential.

The U.S. Government (USG), as part of its continued focus on biosafety and biosecurity, has undertaken a deliberative process to carefully examine the risks and benefits associated with certain GOF studies. The deliberative process involves the National Science Advisory Board for Biosecurity (NSABB), which has been tasked with making recommendations to the USG on this topic, and the National Academy of Sciences (NAS), which was tasked to convene two public symposia to generate broad discussion on the relevant issues. To further inform NSABB deliberations, the National Institutes of Health (NIH) commissioned an independent assessment of the risks and benefits associated with GOF studies and an ethical analysis of the issues related to funding and conducting such studies.

The NSABB was charged with 1) advising on the design, development, and conduct of the risk and benefit assessments for GOF studies, and 2) providing recommendations to the USG on a conceptual approach to the evaluation of proposed GOF studies. The NSABB established two working groups to address its tasks and the full Board convened publically five times between October 2014 and January 2016. 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 risk and benefit assessments.

The working group tasked with issuing recommendations on an approach to evaluating proposed GOF studies considered four major areas: the current policy landscape as it pertains to pathogen research, the results of the risk and benefits assessments, the analysis of relevant ethical issues, and broad stakeholder perspectives on the issues at hand. This working paper describes the working group's process, analysis, preliminary findings, and draft recommendations to date. This paper is not a final NSABB work product and does not represent NSABB recommendations to the U.S. government. This interim report is offered by the working group to the full NSABB, and the broader stakeholder community, to serve as a springboard for discussion at the NSABB meeting in January, 2016.

The working group has developed four key findings:

Key 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 studies—GOF studies of concern—entail risks that are potentially significant enough to warrant additional oversight.

Key Finding 2. The U.S. government has effective policy frameworks in place for 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 studies could be applied.

Key Finding 3. Oversight policies vary in scope and applicability, therefore, current oversight is not sufficient for all GOF studies that raise concern.

Key Finding 4. There are life sciences research studies that should not be conducted on ethical or public health grounds if the potential risks associated with the study are not justified by the potential benefits. Decisions about whether GOF studies of concern 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 and values are also important.

Key Finding 5. The biosafety and biosecurity issues associated with GOF studies are similar to those issues associated with all high containment research, but a small subset of GOF studies have the potential to generate strains with high and potentially unknown risks. Managing risks associated with all high containment research requires Federal-level oversight, institutional awareness and compliance, and a commitment by all stakeholders to safety and security. Biosafety and biosecurity are international issues requiring global engagement.

Based on its analyses thus far, the NSABB working group has formulated the following draft recommendations for discussion:

Recommendation 1. Research proposals involving GOF studies of concern entail the greatest risks and should be reviewed carefully for biosafety and biosecurity implications, as well as potential benefits, 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 working group has proposed a conceptual approach for guiding funding decisions about GOF studies of concern. First, the working group identified the attributes of GOF studies of concern, which are studies that could generate a pathogen that is: highly transmissible, highly virulent, and resistant to public health control measures. Next, the working group identified a set of principles that should guide funding decisions for GOF studies of concern. Only studies that are determined to be in line with these principles should be funded. Additional risk mitigation measures may be required for certain studies to be deemed acceptable for funding.

Recommendation 2. In general, oversight mechanisms for GOF studies of concern should be incorporated into existing policy frameworks. The risks associated with some GOF studies of concern can be identified and adequately managed by existing policy frameworks if those policies are implemented properly. However, the level of oversight provided by existing frameworks varies by pathogen. For some pathogens, existing oversight frameworks are robust and additional oversight mechanisms should generally not be required. For other pathogens, existing oversight frameworks

are less robust and may require supplementation. All relevant policies should be implemented appropriately and enhanced when necessary to effectively manage risks.

Recommendation 3. The risk-benefit profile for GOF studies of concern may change over time and should be re-evaluated periodically to ensure that the risks associated with such research is adequately managed and the benefits are being realized.

Recommendation 4. The U.S. government should continue efforts to strengthen biosafety and biosecurity, which will foster a culture of responsibility that will support not only the safe conduct of GOF studies of concern but of all research involving pathogens.

The working group expects to develop these recommendations further based on additional analysis of the risk and benefit assessments, consideration of ethical issues, and the discussions held at the January 2016 meeting of the NSABB and March 2016 meeting hosted by the National Academies. In Section 7 below, the working group highlights key remaining questions to consider.

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 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 USG response

Experimental techniques and approaches that modify the genome of microorganisms are routinely employed in pathogen research to identify and ascertain the roles of genes and their functional products. Such studies are fundamental to the field of microbial genetics 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 genetic manipulations can result in either diminished (loss-of-function) or enhanced (gain-of-function) biological characteristics that manifest as changes in phenotype.

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 as well. The vast majority of such GOF studies do not raise significant safety or security concerns. However, certain GOF studies involving pathogens have raised significant 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 (see Box 1).

The controversy over certain GOF studies arose 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.[1,2] In 2012, in response to the controversy associated with publishing the manuscripts, 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]

Box 1. Gain-of-Function Studies

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 and microbiology and form the foundation of microbial genetics. Changes to the genome of an organism, whether naturally occurring or directed through experimental manipulations in the laboratory, can manifest as altered phenotypes as biological functions are lost or gained. Such loss- and gain-of-function experiments allow investigators to understand the complex nature of host-pathogen interactions that underlie transmission, infection, and pathogenesis and can help attribute biological function to genes and proteins.

The term "gain-of-function" is generally used to refer to changes resulting in the enhancement or acquisition of new biological functions or phenotypes. This paper further defines "gain-of-function studies of concern" to describe the subset of studies that have been the subject of recent debate regarding potential biosafety and biosecurity implications -- that is, gain-of-function studies with the potential to generate pathogens with enhanced pathogenicity, transmissibility, and ability to evade public health control measures. See Section 5 for more rigorous distinctions.

Concerns regarding laboratory safety and biosecurity associated with GOF studies were renewed following a number of biosafety incidents at U.S. Federal laboratories 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.

As one component of the 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

[1] 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

[2] Herfst 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

such research.[6] The deliberative process involves the National Science Advisory Board for Biosecurity (NSABB), which serves as the official Federal advisory body for providing advice in this area, and the National Academy of Sciences (NAS), which is to foster 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 an analysis of ethical issues surrounding the conduct of such studies. Stakeholder input is also essential to the process and has been received throughout NSABB's deliberative process.

The deliberative process is accompanied by a pause in the provision of new federal funds 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. 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.*[7]

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 ongoing research that involves the types of studies that are subject to the funding restriction above.

NSABB recommendations will inform the USG as it develops policies 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.

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.

[6] U.S. 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

[7] Ibid.

3. NSABB Deliberative Approach

The deliberative process initiated by the USG to evaluate the risks and benefits of GOF studies involves the NSABB and the National Academies. NSABB is developing formal recommendations that address the charge above. The National Academies is convening public forums to generate broad discussions and receive additional stakeholder input on the topic. The National Academies held its first forum early in the deliberative process; its second will be held toward the end. Both are designed to inform NSABB deliberations.

To inform the deliberative process further, NIH commissioned two additional analyses: 1) qualitative and quantitative risk and benefit assessments, to be conducted by Gryphon Scientific, and 2) a review of the ethical considerations associated with the GOF issue and an analysis of ethical decision-making frameworks that might be considered by the NSABB when developing its recommendations, to be conducted by Professor Michael Selgelid. The overall deliberative process is illustrated in Figure 1.

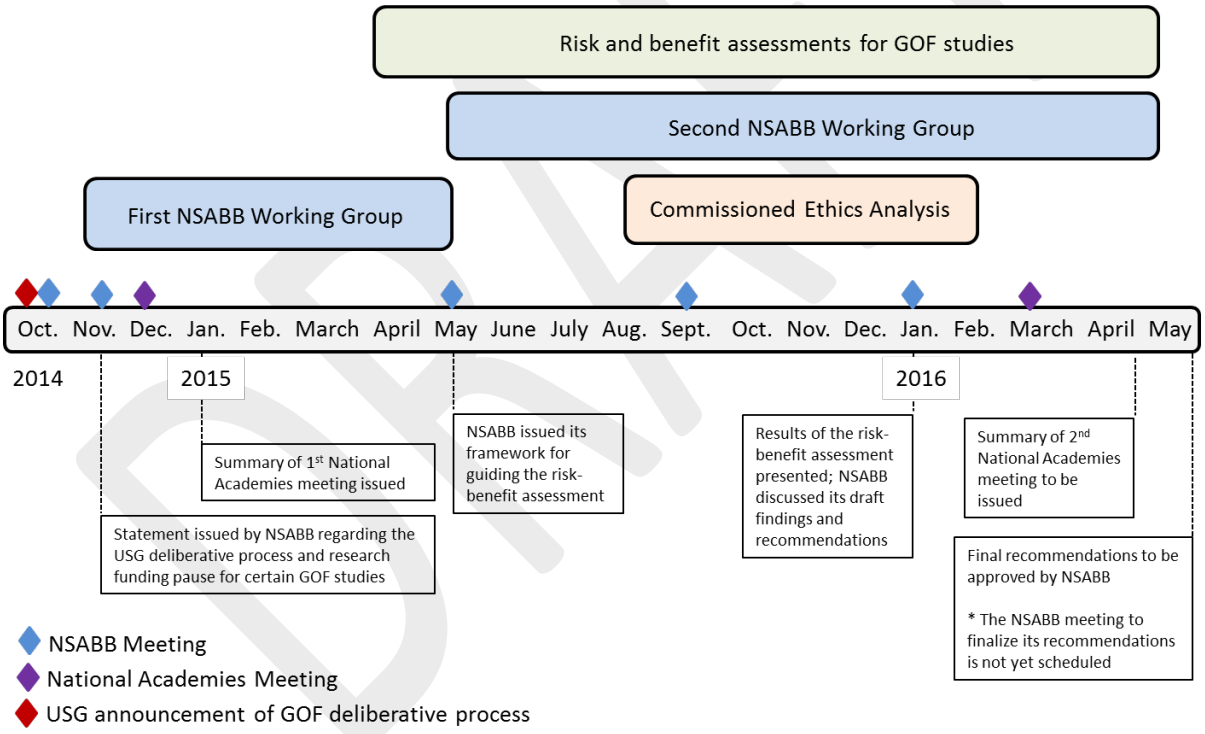

Figure 1. Timeline and major events of the GOF deliberative process.

The NIH Office of Science Policy, which administers the NSABB, managed the NSABB's overall deliberative process. NIH oversaw the work of its contractors, Gryphon and Michael Selgelid, and interfaced between the NSABB and contracted entities. NSABB recommendations will ultimately be considered by the U.S. government as it formulates policy in this area.

See Appendices A, B, C, and E for the NSABB and working group rosters, a detailed description of the NSABB's deliberative approach, an overview of different stakeholder views that were considered, and a list of the experts and sources consulted, including public comments that were received.

4. Analysis

The NSABB working group tasked with developing recommendations on a conceptual approach for evaluating GOF proposals examined three major areas: the current policy landscape for overseeing research involving pathogens, ethical issues associated with funding and conducting GOF studies, and the results of Gryphon's risk and benefit assessments. In addition, the NSABB and the NSABB working group considered broad stakeholder perspectives through expert consultations, review of the National Academies workshop proceedings, analysis of published articles, and comments from attendees at NSABB meetings and submitted to the NSABB. The NSABB working group's preliminary analysis and findings are described below. The NSABB working group began by developing principles to guide its deliberations.

4.1. Guiding Principles for NSABB Deliberations

The principles below were developed to guide the NSABB's deliberations and underpin its analysis of the risk and benefit assessments and the Board's forthcoming recommendations.

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.

4.2. Analysis and Interpretation of the Risk and Benefit Assessments

The NSABB working group has reviewed the risk and benefit assessments conducted by Gryphon Scientific, which were designed to evaluate the risks and benefits of GOF research in a broad way so as to encompass both benign and worrisome aspects of a broader range of GOF studies than those that have raised concern. The RBA was designed to examine the risks and benefits associated with GOF studies that are currently being conducted as well as those that might be conducted in the near future. The RBA analyzed biosafety and biosecurity risks as well as several categories of possible benefits. Overall, the RBA includes a commendable amount of sophisticated work and analysis, is generally well-done, and achieves the goals it was intended to address. That said, NSABB welcomes public input and debate on the conduct of the risk and benefit assessments. The report describing the risk and befit assessments was made publically available in December, 2015.[8]

Strengths of the RBA

The RBA has numerous significant strengths. It is a thorough and extensive analysis of the risks and benefits of GOF work in the context of the guidance posed in the NSABB *Framework for Conducting Risk and Benefits Assessments of Gain-of-Function Research* (May 2015). The overall approach takes into

[8] Risk and Benefit Analysis of Gain-of-Function Research, Final Draft Report. Gryphon Scientific, December, 2015. http://osp.od.nih.gov/sites/default/files/Risk%20and%20Benefit%20Analysis%20of%20Gain%20of%20Function%20Research%20-%20Draft%20Final%20Report.pdf

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*. A few items from the *Framework* were eliminated from consideration as a result of discussions that took place at the meeting of the NSABB where the framework was voted on; this was done so that the most probable issues of concern could be thoroughly addressed within the available time and resources.

The biosafety risk assessment does a credible job of defining the relative risks associated with potential laboratory accidents involving GOF manipulations or pathogens with enhanced characteristics as compared to research with wild-type pathogens. This analysis is performed in a semi-quantitative way; it uses appropriate, established, peer-reviewed methods to the extent available. The parametric approach employed is powerful and allows almost any situation of interest to be considered, if desired.

The report does effectively illustrate that the negative 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 global population). The working group recognizes that analyzing low-probability, high-consequence events for which little data exists is challenging and appreciates any attempt to make this point clear. In addition, there are also limitations associated with the estimation of the probabilities of accidents that initiate the chain of events that could result in a loss of containment (see Limitations of the RBA below).

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, which was conducted and presented separately) is a qualitative analysis of risks that may result from the misuse of information derived from GOF studies with influenza, MERS, and SARS that have already been published and 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 benefits of GOF studies, a difficult task without much prior methodology to draw upon. The results are not quantitative and attempts to quantify 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 did a good job of analyzing the possible benefits of alternatives to GOF studies and fairly clearly identified 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 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 coronaviruses) 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 and reasonable, and generally extensively documented.

Limitations of the RBA

The RBA also has some weaknesses and limitations that should be noted. 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 or regarding events such as laboratory accidents or security breaches, or possible future acts of terrorism are limited in some cases and are in principle unavailable 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, not absolute values, for the risks associated with laboratory accidents involving GOF studies. This may be adequate for some comparisons but inadequate for others. For instance, 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 miniscule 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 may, in fact, be concerning. Additionally, differences in risk that are relatively small (~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. However, the lack of comprehensive estimates of baseline risk make interpreting the biosafety risks a challenge.

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 should be kept in mind as any conclusions are reached.

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 the number of infections that could occur if a pathogen with various enhanced characteristics were intentionally released. However, this analysis assumes that 1 or 10 individuals are initially infected as a result of bioterror with no indication of how likely such an event would be, since there is no way to make such an estimate based on existing data. Similar to the discussion above, estimating risk by understanding consequences without their likelihood is challenging.

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 was extensive, evaluation of risks of alternative approaches was not as thorough. In addition, risks and benefits have not been 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.

Finally, in most cases the wild-type comparator for pandemic influenza was the 1918 strain. Thus, the wild type risks are relatively high, and this may obscure significant risks associated with GOF studies that would be more apparent if the wild-type strain was a less virulent (and more typical) pandemic strain. A GOF study that risked triggering an event as serious as the 1918 influenza pandemic, or even a somewhat less serious pandemic, would still be a source of major potential concern.

Key Results of the RBA

While the working group has examined all of the analyses in the RBA, some results are important to highlight. In general, the working group 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. 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-generated 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, no GOF-generated phenotypes led to greatly increased risk, but that is based on using 1918 influenza as the comparator; because the risk associated with the wild-type 1918 strain is already so great it is difficult to increase risk substantially. If less transmissible and/or less virulent wild-type strains were used as the basis of comparison, the risks of GOF studies with pandemic strains might appear higher. 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 of the Executive Summary of Gryphon's RBA report.

In general, GOF studies that were not considered by the working group 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 or immune evasion 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. Interestingly, the risks associated with information from future GOF studies with influenza, SARS and 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 agents of harm is readily available.

Most GOF studies provide benefits in the form of new scientific knowledge, and many of these benefits are unique (i.e., unable to be achieved by alternative, non-GOF approaches). While GOF studies are likely to provide some 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 situation is experiments that increase growth of seasonal influenza vaccine candidates in culture; these studies provide unique benefits to current production of seasonal flu vaccines, and likely will in the future. Another reasonably clear unique benefit is derived from experiments that enhance mammalian pathogenicity for coronavirus 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 with 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 pathogens with several GOF phenotypes that may be valuable for surveillance and preparedness efforts, although other scientific advances are needed to fully realize the benefits. Additionally, a variety of benefits were identified that may also be provided to some extent by alternative approaches.

4.3. Consideration of Ethical Values and Decision-Making Frameworks

The risk and benefit assessments provide quantitative and qualitative information about the potential risks and benefits associated with conducting GOF research. However, determinations about whether such studies should be undertaken will involve value judgments to assess the risks and benefits and make policy judgments. A number of substantive values (i.e., those that guide decision-making about research) and procedural values (i.e., those that guide the process of decision-making about research) 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,[9] the literature on public health ethics,[10] and the literature on oversight of emerging technologies,[11] as well as the literature specifically debating appropriate approaches to overseeing DURC and GOF research that has raised concern.[12,13,14] The commissioned ethics analysis conducted by Michael Selgelid also describes additional decision-making frameworks and values to be considered.[15]

Substantive values

The following values are those that apply to decision-making about research and may be important to consider when funding a research proposal involving gain-of-function studies of potential concern, that is, those that might entail significant risks.

Non-maleficence: not causing harm. Harm might include: losing lives; causing disease; damage to the economy, national or international security, or agriculture; or loss of public trust in science or governance structures. There are inherent risks associated with research involving pathogens that could result in harm. Approaches aimed at preventing harm and mitigating potential risks should be considered and applied to the design, conduct, and communication of research involving pathogens in GOF studies.

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: saving lives, preventing disease, improving public health; enhancing the economy, national and international security, or public trust in science and

[9] 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

[10] Kass NE. 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/

[11] 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

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

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

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

[15] Selgelid, Michael. Gain-of-Function Research: Ethical Analysis. December 7, 2015. http://osp.od.nih.gov/sites/default/files/GOF%20%20White%20Paper%20by%20Michael%20Selgelid_0.pdf

governance structures. When the ultimate goals of the research are to improve public health, public health ethics would ask how effective the research is likely to be in achieving those goals, what are the known or potential burdens of the research, can those burdens be minimized, whether there are alternative approaches that are less risky or burdensome, and how can the potential benefits and burdens of the research be fairly balanced. The work of the Presidential Commission for the Study of Bioethical Issues suggests that those formulating and effectuating 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."[16] 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,[17] to name but 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. Those who will potentially be exposed to risk, through participation in research or other avenues of exposure, should be selected equitably.

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.

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 is compatible 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 Presidential Commission

[16] 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
[17] Nozick R. Anarchy, State, and Utopia. New York: Basic Books, 1974.

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."[18]

Responsible Stewardship: acting in a way that shows concern for children, future generations, and the environment. The Presidential 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."[19]

Procedural Values

The following values are those that apply to the process of decision-making about research and may be important to consider when establishing mechanisms to review and/or approve the funding of research proposal involving gain-of-function studies of potential concern, that is, those 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 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 life sciences 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 Presidential 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."[20]

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 a decision, including uncertainties, controversies, and limitations of analyses. Transparency is an important

[18] 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.
[19] Ibid., p5.
[20] Ibid., p5.

part of accountability and public participation. It allows review and reconsideration of policy over time as new facts emerge and analysis evolves.

Decision-Making Strategies for Evaluating and Managing Risks

A number of decision-making strategies can be employed when making decisions related to the ethical evaluation and management of risks. Different strategies reflect different attitudes toward risk-taking. These and other strategies are discussed in Michael Selgelid's commissioned paper.[21]

Maximax: choose the option with the best possible outcome. Maximax is a 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.

Expected Utility Theory: choose the option that maximizes expected utility, where expected utility for a possible outcome = probability x utility. Expected utility theory involves a balancing of risks and benefits. Cost-benefit analysis in economics is a form of expected utility theory. One of the problems with expected utility theory is that one may not always have sufficient evidence to confidently estimate the probabilities involved in the utility calculus. When this is the case, other approaches may be appropriate.

Maximin: choose 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 may present difficulties in 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 lead to good and bad outcomes, strict adherence to maximin would imply a very cautious approach to science and technology development.

Precaution: take 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 if "plausible" if we have some scientific evidence that it could occur even if we cannot confidentiality estimate the probability of the risk. There are many versions of the precautionary principle, including ones that more or less risk-averse.[22,23]

[21] Selgelid, Michael. Gain-of-Function Research: Ethical Analysis. December 7, 2015. http://osp.od.nih.gov/sites/default/files/GOF%20%20White%20Paper%20by%20Michael%20Selgelid_0.pdf
[22] Resnik DB. Environmental Health Ethics, New York: Oxford University Press, 2013.
[23] Munthe C. The Price of Precaution and the Ethics of Risks. Dordrecht: Springer, 2011.

4.4. Examination of the Current Policy Landscape

Many Federal 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 D.

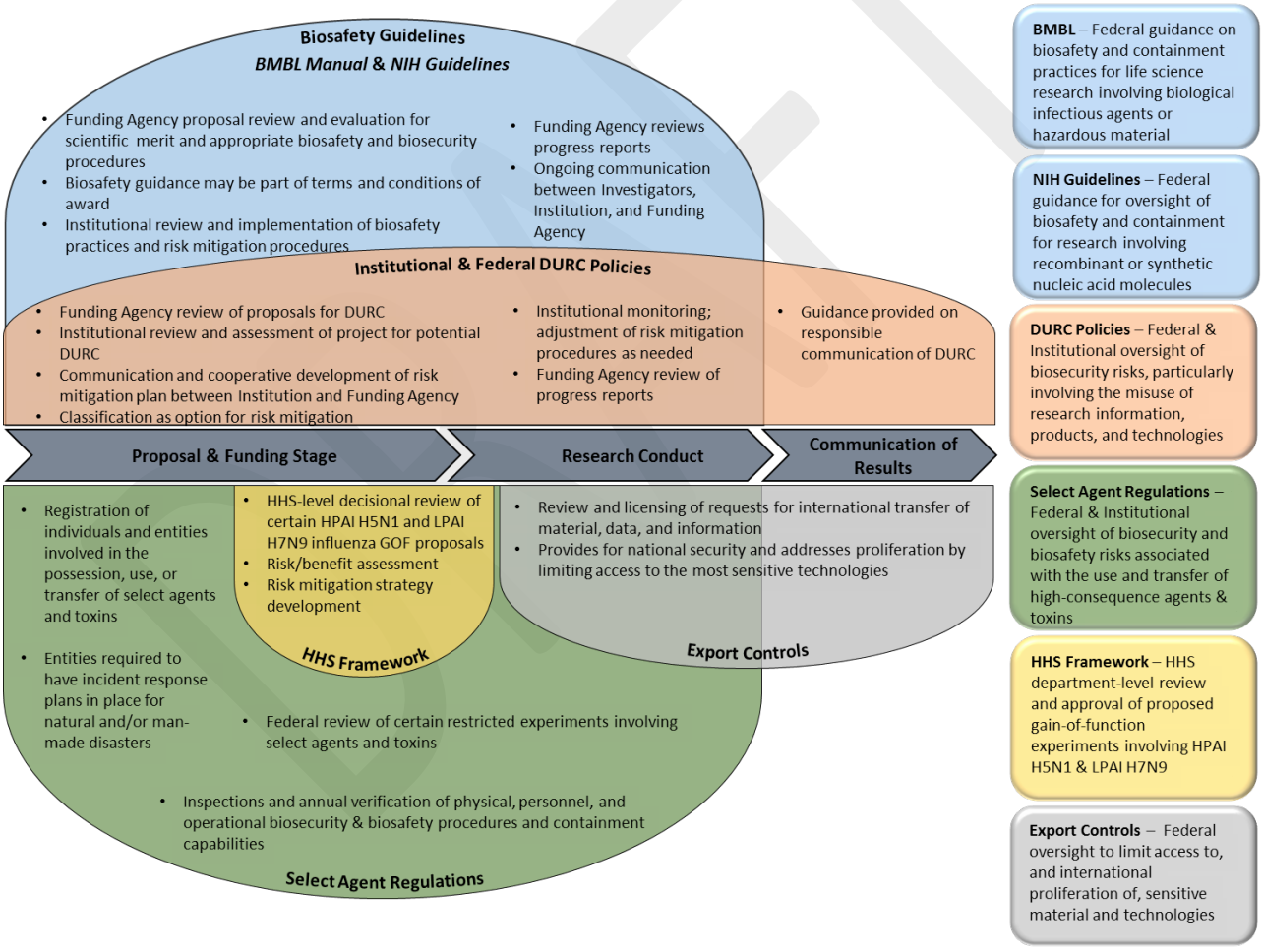

Figure 2. U.S. government oversight of life sciences research involving pathogens. Oversight policies apply at different stages and occur at different levels throughout the research life cycle. See text and Appendix D for descriptions of each policy. The policies depicted in this figure are defined by different applicability and scope requirements 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 U.S. government 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 peers 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 boards, specific to individual funders within NIH, to determine how proposals fit within the broader strategic objectives of the funder.

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*), the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (NIH Guidelines), 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 CDC-NIH guidance document that is generally considered the authoritative reference for laboratory biosafety. It describes the fundamentals of biological containment, which includes 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 the public health.

Analysis: 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. The BMBL does not address gain-of-function 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.[24]

The BMBL is not a regulatory document. U.S. funding agencies may require it be followed as a term and condition of awards 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 recombinant or synthetic nucleic acid research conducted at or sponsored by institutions that receive NIH funding for any such research. Compliance with the *NIH Guidelines* is typically required as a term of award of funding. Other Federal agencies may also require compliance with the *NIH Guidelines*. Certain higher risk experiments require review by the Recombinant DNA Advisory Committee (RAC)[25] 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 know to acquire the trait naturally, if such acquisition could compromise the ability to control disease agents in humans, veterinary medicine or agriculture.

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* specifies 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*.

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

[24] 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]

[25] 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

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 transmissible among mammals by respiratory droplets.

Analysis: The *NIH Guidelines* issue detailed biosafety guidelines that are required to be followed as a term and condition of award. These guidelines include mechanisms for being periodically updated based on input received from an external advisory body, the RAC. They also provide for higher level scrutiny (i.e., major actions) of experiments that may entail significant risks. The *NIH Guidelines* have been updated to address biocontainment and biosafety practices associated with certain GOF studies involving HPAI H5N1 viruses, as well as general guidance for research involving other influenza viruses.

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 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. Therefore, some GOF studies may not be subject to the *NIH Guidelines* depending on their funding source (or whether the institution where the research is being conducted is subject to the *NIH Guidelines*).

The Federal Select Agent Program

Subtitle A and B of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 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 Select Agent Program (SAP) is administered jointly by the HHS Centers for Disease Control and Prevention and USDA Animal and Plant Inspection Service. The SAP 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 SAP 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 Intragovernmental Select Agent and Toxin Technical Advisory Committee serves as an advisory group to the SAP. In the wake of the recent laboratory incidents at Federal facilities involving select agents, two advisory committees have issued recommendations for ways to strengthen the Select Agent Program.[26] [27] Plans to implement these recommendations are also in place.[28]

Analysis: The SAP addresses physical and personnel security issues associated with certain pathogens that, if misused by individuals with malevolent intent, could pose the greatest threat to public health or national security. Some security measures and other requirements of the SAP also provide biosafety oversight. All entities that possess, use, or transfer select agents must abide by the select agent regulations, regardless of the source of funding for conducting research or related activities with the agents. Studies that could be considered GOF studies are subject to oversight by the SAP 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 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. 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 SAP (though they could be subject to Federal and institutional biosafety oversight).

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

The U.S. government has issued two Federal policies for the oversight of life sciences DURC. These policies focus oversight on research involving 15 high-consequence pathogens and toxins[29] that involve seven categories of experimental activity, which are projects that can be reasonably anticipated to:

[26] Report of the Federal Experts Security Advisory Panel, U.S. Government, December 2014.
[27] Fast Track Action Committee Report: Recommendations on the Select Agent Regulations Based on Broad Stakeholder Engagement, U.S. Government, October 2015.
[28] 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
[29] The agents within the scope of the USG DURC policies are the 13 Tier 1 select agents plus HPAI H5N1 and 1918 influenza virus.

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.

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.[30]

The DURC policies outline a coordinated approach to oversight between the Federal funding agencies and institutions that conduct such research. The policy for Federal oversight, issued in March 2012, requires Federal agencies to review proposed and ongoing research projects to identify any that constitute DURC. 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 is established to ensure that DURC is communicated in a responsible manner. Federal funding agencies can provide advice and guidance on responsible communication, but

[30] 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."

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 projects that might involve these effects are only subject to DURC oversight if the study involves one of the 15 agents listed in the policy. Only two influenza viruses are listed within the scope of these policies; SARS and MERS coronaviruses are not listed.[31] The DURC policies are also inherently subjective. While the list-based approach clearly delineates projects that are subject to oversight, the definition of DURC, and to a lesser extent, the seven experimental effects, all require significant judgment and interpretation.

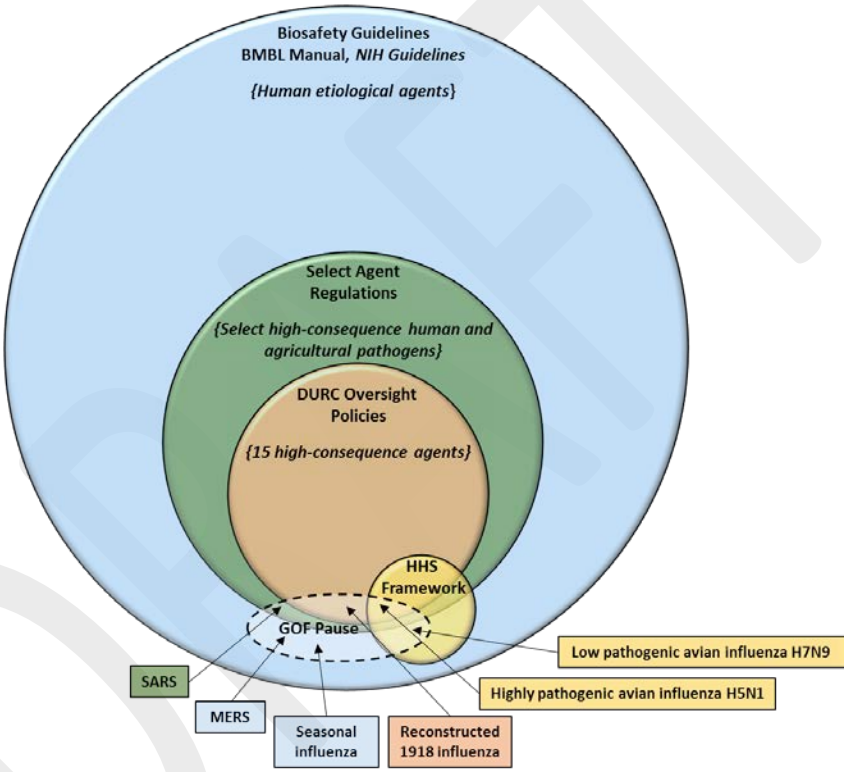

Figure 3. Comparison of the scope of different policies for the oversight of life sciences research involving pathogens. Oversight policies apply to research involving specified agents or procedures. GOF studies involving pathogens or manipulations covered under a given policy would be subject to oversight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

[31] 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.

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

The only U.S. Federal 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 the U.S. Department of Health and Human Services in February, 2013. Under the *HHS Framework*[32,33] 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 approval before being funded by HHS. This policy was subsequently expanded to include review of similar proposals involving low pathogenic avian influenza H7N9 virus.[34]

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 the Federal 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 up front and make recommendations about risk mitigation—including consideration of alternative approaches or modifying the experimental design—at the outset. This review process

[32] *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

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

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

also involves broader expertise including, ethical, legal, security, intelligence, and more. The criteria that must be met in order to receive funding are subject to judgment and interpretation. The scope of the *HHS Framework* is 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 do not receive this pre-funding review.

Reviews under this framework are conducted by a group internal to the USG and therefore, are not transparent. Reviewing GOF studies in a confidential setting allows for the examination of potentially sensitive scientific, proprietary, and personal information, and allows discussions that may be sensitive from a national security or public health preparedness perspective. However, such reviews also make it difficult to independently assess the effectiveness of the review. Finally, the *HHS Framework* was in 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, 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, often 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 has 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 considers 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 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 how effective this approach is. However, it is considered promising.

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.[35] Life sciences research that requires classification is classified at its outset and conducted in 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 infeasible.

Export controls are Federal regulations that restrict 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 is considered to be an export to that foreign national's country. The regulations are complex but, in general, they specify which items, when shipped to which destinations, will require export licenses. 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.[36] However, some might fall under the jurisdiction of the State Department's International Traffic in Arms regulations.[37]

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.[38,39] 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.[40] The U.S. government, in most cases, has no authority to mandate redaction, restriction, or classification of a scientific publication

[35] 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

[36] 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

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

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

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

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

that it does not own or control, and the development of a mechanism for restricting communication of unclassified information to only those who require access, remain challenging and to date, unsuccessful.[41]

Analysis: While information and products associated with scientific research could be misused to cause harm, managing information risks at the publication stage is difficult. 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 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 entail that these studies be conducted in significantly different settings than they are conducted 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 could, on security grounds, decide 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.

4.5. Potential Policy Approaches and Options

Emerging technologies are challenging current policy frameworks. This is particularly relevant for GOF studies. Reagents and equipment are becoming cheaper, giving more people access to the tools needed to conduct life sciences research. There are more options for private funding, including crowd-sourced online funding, for research and projects. Research findings can be self-published online or posted with little or no peer-review on open access pre-print servers. In general, these are exciting developments for science, but they also present challenges since the traditional points where oversight might be applied are changing.

The working group considered a number of policy approaches that could be applicable to GOF studies that have raised concerns. The working group used ideas from a number of frameworks to inform its findings and deliberations.

Permissive approach. A permissive approach, in general, would allow an activity unless the environment, health, or security, are clearly compromised. This approach may reduce unnecessary

[41] 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.

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.

Precautionary approach. 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 entail restricting GOF studies of potential concern unless they are demonstrated to be safe.

Planned adaptation or risk-based approach. A planned adaptation approach provides a systematic approach to deal with managing risks in the face of uncertainty. It involves: 1) preparation to identify the risks and regulatory gaps, including getting 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 effects of policies; and 4) updating and revising policy 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.[42] For GOF studies, this approach might entail allowing GOF studies of potential concern—or certain GOF studies—to proceed under defined conditions, then evaluating the risks-benefit landscape to determine whether the GOF studies that are permitted should continue, be expanded, or be restricted.

Threshold approach. This approach would entail creating a risk threshold beyond which, certain studies are given special attention or subject to additional scrutiny or oversight. This approach 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 of potential concern, this would 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. This approach would involve 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 of potential concern this might involve requiring that certain studies only be conducted in facilities with certain biocontainment conditions, biosafety practices, and security measures.

[42] 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

5. Findings

In developing the findings below (Box 2), the NSABB working group considered the results of (i) the risk and benefit assessments, (ii) policy analysis, (iii) discussions of ethics to date, and (iv) the perspectives of stakeholders.

Box 2. Summary of Key Findings

Key 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 studies—GOF studies of concern—entail risks that are potentially significant enough to warrant additional oversight.

Key Finding 2. The U.S. government has effective policy frameworks in place for 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 studies could be applied.

Key Finding 3. Oversight policies vary in scope and applicability, therefore, current oversight is not sufficient for all GOF studies that raise concern.

Key Finding 4. There are life sciences research studies that should not be conducted on ethical or public health grounds if the potential risks associated with the study are not justified by the potential benefits. Decisions about whether GOF studies of concern 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 and values are also important.

Key Finding 5. The biosafety and biosecurity issues associated with GOF studies are similar to those issues associated with all high containment research, but a small subset of GOF studies have the potential to generate strains with high and potentially unknown risks. Managing risks associated with all high containment research requires Federal-level oversight, institutional awareness and compliance, and a commitment by all stakeholders to safety and security. Biosafety and biosecurity are international issues requiring global engagement.

<u>Key Finding 1</u>: There are many types of GOF studies and not all of them have the same level of risks. Only a small subset of GOF studies—GOF studies of concern—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. Research involving pathogens with pandemic potential are generally considered to involve the greatest risks because a laboratory accident that were to result in an infection of a lab worker (or other release) could potentially release a pathogen that could spread rapidly and efficiently through the human population. A laboratory pathogen with enhanced characteristics could, 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.

Research involving pathogens that are highly virulent, transmissible by the airborne route, and for which there are no available countermeasures or population immunity would be of greatest concern because public health and control options would be limited for such a pathogen, in the event of a loss of containment event to occur. 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.[43] As discussed in section 4.2 of this paper, risks associated with some pandemic influenza strains such as 1918 are already high and thus may be difficult to increase significantly. However, increased transmissibility, increased pathogenicity, and evasion of medical countermeasures have the greatest potential to increase risk; in some strains even a moderate increase might be a concern. The greatest concern associated with studies involving the generation of pathogens with pandemic potential would be the intentional or accidental release of a highly transmissible, highly virulent pathogen to which a significant proportion of the global human population is susceptible.

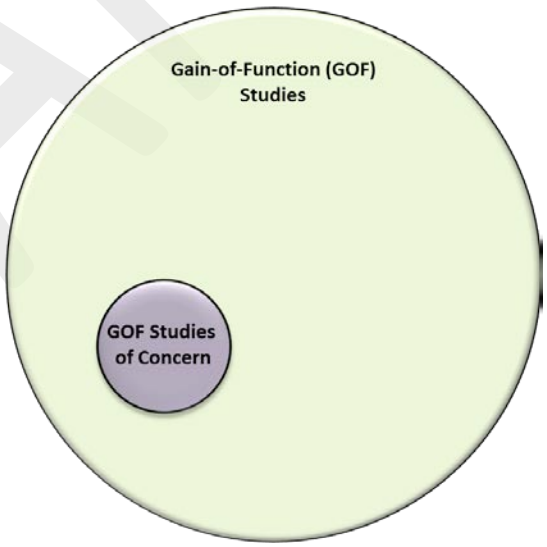

Figure 4. Conceptual categorization of GOF studies involving human or animal pathogens. GOF studies include a broad range of experimental approaches, most of which do not raise significant concerns. GOF studies of concern represent a small subset of all GOF research that can be reasonably anticipated to result in generation of a pathogen that is highly transmissible, significantly virulent, and likely to be resistant to control measures.

To help categorize studies based on the level of concern stemming from their associated risks, the working group has described studies as: GOF studies and GOF studies of concern (Figure 4). The term "GOF studies" would encompass all studies involving human or animal pathogens

[43] Risk and Benefit Analysis of Gain-of-Function Research, Final Draft Report. Gryphon Scientific, December, 2015. http://osp.od.nih.gov/sites/default/files/Risk%20and%20Benefit%20Analysis%20of%20Gain%20of%20Function%20Research%20-%20Draft%20Final%20Report.pdf

whereby some characteristic of the pathogen is enhanced. The vast majority of GOF studies do not raise any significant concerns; these studies do not entail novel or significant risks and are subject to layers of oversight to manage risks. "GOF studies of concern" represent the small subset of studies that result in the generation of a pathogen that is highly transmissible, significantly virulent, and likely to be resistant to public health control measures. GOF studies of concern are those that could generate a pathogen with pandemic potential.

Key Finding 2. The U.S. government has effective policy frameworks in place for 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 studies could be applied.

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 apply oversight and help manage risks at several points throughout the research life cycle including the proposal review, the funding decision, the time during which the research is being conducted, 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, institutional review and compliance committees, individual investigators, federal advisory committees, and journal editors.

Key Finding 3. Oversight policies vary in scope and applicability, therefore, current oversight is not sufficient for all GOF studies that raise concern.

As noted in section 4.4, some U.S. policies are applicable to some, but not all GOF studies of concern. Risks associated with GOF studies of concern that do not involve select agents or pathogens subject to oversight under the USG DURC policies of the HHS Framework, would largely be managed at the institutional level, in accordance with guidance in the *NIH Guidelines* and BMBL. GOF studies of concern that are not be conducted with U.S. government funds are not subject to oversight by a Federal funding agency (unless the work involves a select agent, whose oversight is articulated in Federal statute and requires compliance from all researchers and institutions, regardless of their funding source). Other countries fund and conduct life sciences research, including GOF studies, which are beyond the purview of the U.S. government as well.

Full compliance with policies is essential to their effectiveness. In addition to a commitment to proper implementation and enforcement at the Federal and institutional levels, the effectiveness of policies can be enhanced by training, education, codes of conduct, and other mechanisms, which are valuable tools for continuing to build a culture of responsibility among researchers.

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 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 and for informing policy development. The DURC policies and the *HHS Framework* do not have mechanisms articulated for seeking input on policy development, reviewing, or updating the policies, though both state an intention to be updated as necessary.

Key Finding 4. There are life sciences research studies that should not be conducted on ethical or public health grounds if the potential risks associated with the study are not justified by the potential benefits. Decisions about whether GOF studies of concern 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 and values are also important.

There are life sciences research studies that should not be conducted for ethical reasons. Examples of studies that should not be conducted are those that involve human subjects who have not provided consent, studies that are anticipated to cause undue harm to a human subject, or studies that entail benefits that are unjustifiable in the light of the risks. For example, the development of biological weapons is unethical and has been banned by international treaty.[44]

There may be GOF studies that should not be funded on ethical grounds but it is difficult to identify or describe such studies, particularly 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 unintended consequences that could be foreseen. While the risks associated with a particular manipulation of a pathogen could be estimated, any determination about whether to conduct the study must also incorporate an evaluation of the potential benefits. 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

[44] 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/

more or less likely to be realized based on other enabling factors, such as new scientific findings or technologies. Decisions to fund GOF studies that entail risks must be made with an evaluation of the risks and benefits as they are understood and can be predicted at the time the decision is being made. General principles that describe what is acceptable and not acceptable for funding may be more effective at guiding funding decisions about GOF studies than specific descriptions of GOF experiments.

The working group did not seek to develop a list of studies that should not be conducted but the issue was discussed on numerous occasions. One example of a scientific study that should not be conducted might be: Insertion of a virulence gene from an unrelated organism into the genome of a respiratory transmissible virus, which would never occur by natural recombination. This study, and others that the working group considered as being ones that potentially should not be funded on ethical grounds, would appear to lack public health benefit, since the pathogen could not naturally arise and would entail unnecessary risks.

Key Finding 5. The biosafety and biosecurity issues associated with GOF studies are similar to those issues associated with all high containment research, but a small subset of GOF studies have the potential to generate strains with high and potentially unknown risks. Managing risks associated with all high containment research requires Federal-level oversight, institutional awareness and compliance, and a commitment by all stakeholders to safety and security. Biosafety and biosecurity are international issues requiring global engagement.

All properly managed high containment research, including the majority of GOF studies, mitigate biosafety and biosecurity risks through engineering controls, laboratory practices, medical surveillance and support, appropriate training, and documented staff competence. However, GOF studies of concern have the potential to generate strains with significant and/or unknown risks that may require additional oversight and containment mechanisms.

In addition, the potential risks and benefits associated with GOF studies are international in nature; laboratory accidents or intentional misuse could have international consequences, and relevant benefits for vaccine and other countermeasure development or disease surveillance, would likely have important international implications. In addition, the research enterprise is international in nature and GOF studies are conducted in several countries already. While U.S. government policy regarding GOF studies will only directly affect domestic and international research supported by the U.S. government, decisions by the United States in this area may influence GOF oversight policies globally. International perspectives are also important to the development of U.S. policy in this area. Global engagement is necessary to foster an international culture of responsibility around research involving dangerous pathogens, including GOF studies of concern.

6. Draft Recommendations for Discussion

Based on its analyses thus far, the NSABB working group has formulated the following potential recommendations. The working group notes that these recommendations are preliminary in nature and offers them to stimulate discussion. The working group expects to develop these recommendations further based on additional analysis of the risk and benefit assessments, consideration of ethical issues, and discussions held at the January 2016 meeting of the NSABB and March 2016 meeting hosted by the National Academies.

Box 3. Summary of Draft Recommendations for Discussion

Recommendation 1. Research proposals involving GOF studies of concern entail the greatest risks and should be reviewed carefully for biosafety and biosecurity implications, as well as potential benefits, 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. In general, oversight mechanisms for GOF studies of concern should be incorporated into existing policy frameworks. The risks associated with some GOF studies of concern can be identified and adequately managed by existing policy frameworks if those policies are implemented properly. However, the level of oversight provided by existing frameworks varies by pathogen. For some pathogens, existing oversight frameworks are robust and additional oversight mechanisms should generally not be required. For other pathogens, existing oversight frameworks are less robust and may require supplementation. All relevant policies should be implemented appropriately and enhanced when necessary to effectively manage risks.

Recommendation 3. The risk-benefit profile for GOF studies of concern may change over time and should be re-evaluated periodically to ensure that the risks associated with such research is adequately managed and the benefits are being realized.

Recommendation 4. The U.S. government should continue efforts to strengthen biosafety and biosecurity, which will foster a culture of responsibility that will support not only the safe conduct of GOF studies of concern but of all research involving pathogens.

Recommendation 1. Research proposals involving GOF studies of concern entail the greatest risks and should be reviewed carefully for biosafety and biosecurity implications, as well as potential benefits, 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.

The working group has described GOF studies of concern as those that can be reasonably anticipated to generate a pathogen that exhibits, to a significant degree, all of the characteristics below. These characteristics are intended to help funding agencies and research institutions identify GOF studies of concern and to assist in consideration of whether such studies should be funded and what oversight might be required.

Research proposals that can be reasonably anticipated to involve a GOF study of concern, as defined as a study that could generate a pathogen with all of the following attributes, should be reviewed carefully prior to determining whether it is appropriate to be funded:

i. **The pathogen generated is highly transmissible in a relevant mammalian model.**
Laboratory pathogens of greatest concern are those that would be expected to have the ability to transmit efficiently among mammalian hosts that serve as a proxy for human infections, particularly by the respiratory route. To be considered a GOF study of concern, the resulting pathogen would need to be anticipated (based on scientific evidence and/or expert judgment) to have the potential for sustained secondary transmission among humans.

ii. **The pathogen generated is highly virulent in a relevant mammalian model.**
Laboratory pathogens of greatest concern are those that would be expected to be highly virulent, causing significant morbidity or mortality in mammalian hosts that serve as a proxy for human infections. To be considered a GOF study of concern, the resulting pathogen would need to be anticipated (based on scientific evidence and/or expert judgment) to have the potential for causing significant consequences in humans, such as severe disease symptoms or a high case fatality rate.

iii. **The pathogen generated is likely resistant to control measures or more capable of being spread among human populations than currently circulating strains of the pathogen.**
This characteristic could be conferred to a laboratory pathogen in a number of ways such as: incorporating resistance to medical countermeasures; altering its host range to include mammals for a pathogen that humans would lack population immunity; significantly altering the pathogen to evade host immunity; modifying the pathogen in such a way that it could be anticipated to suppress an immune response in humans. To be considered a GOF study of concern, the resulting pathogen would need to be anticipated (based on scientific evidence and/or expert judgment) to spread efficiently through human populations with no options for controlling its spread other than isolation or quarantine. Vaccines and countermeasures would be unavailable (or in quantities such that their widespread use would be impossible) or have minimal effectiveness.

By definition, all human pathogens have the ability to cause morbidity and mortality in humans. However, the degree to which a pathogen can spread among humans and the severity of its symptoms can vary greatly. The characteristics above are intended to assist in the identification of GOF studies that might generate pathogens with a combination of all three attributes that would raise unique or significant concerns.

Importantly, a proposed experiment need not involve the simultaneous enhancement of all three phenotypes in a single step to generate a pathogen with the characteristics above. Rather, any proposed experiment that could result in the generation of a pathogen with all three attributes would be a GOF study of concern. For instance, research involving a pathogen that starts with two of the above attributes would raise concern if a study were anticipated to confer the third characteristic to the agent (while retaining the other two). Other studies may generate a pathogen with the above characteristics after a series of manipulations that enhance the phenotypes separately but ultimately result in a pathogen with all three attributes. Any route of experimentation that is anticipated to ultimately generate a pathogen that exhibits all three of the characteristics above would raise concern and should be reviewed carefully before it is determined to be appropriate to receive funding.

Of note, the generation of pathogens that exhibit one or two of the characteristics above, or all three but only mildly, still entail risks but the risks associated with such studies are generally managed through existing biosafety and biosecurity oversight frameworks. The characteristics above are intended to facilitate the identification of the small subset of projects considered GOF studies of concern.

The NSABB working group has identified examples that could be anticipated to generate a pathogen with the attributes described above:

i. An experiment that is anticipated to generate avian influenza viruses that are airborne transmissible in mammals if the starting virus is pathogenic in humans because the pathogen would gain more efficient mammalian transmission and there is no existing population immunity in humans.

ii. Reassortant studies involving avian and human influenza strains where strains that could be pathogenic and transmissible in mammals are selected for, or could be anticipated, and where the antigenicity of the resulting strains is expected to remain avian-specific, such that human populations would not be expected to have been exposed to such a strain.

iii. Studies utilizing a strain of SARS-CoV, or some other emerging human pathogen, which will be modified in ways that can be anticipated to render humans more susceptible to infection by for instance, introducing resistance to a countermeasure (were countermeasures available).

The NSABB working group has identified examples that would not be anticipated to generate a pathogen with the attributes described above:

i. Studies aimed at generating a mouse-adapted MERS-CoV, or other emerging human pathogen, would not be captured by the above criteria because although the resulting virus could be transmissible and potentially pathogenic in humans, humans would be no more susceptible to the virus than those that are naturally-circulating.

ii. Studies enhancing the growth of attenuated seasonal influenza viruses because, while increasing the virus's ability to replicate could potentially result in its increased ability to cause disease, the resulting virus would not be anticipated to be more transmissible or resistant to countermeasures or other control measures and therefore would not meet the second and third criteria.

iii. Antigenic drift studies of seasonal or pandemic influenza would not be captured because such studies are not anticipated to increase the pathogenicity or transmissibility of the viruses above levels that are currently observed in nature.

The working group envisions that proposals anticipated to involve GOF studies of concern, as described by the three characteristics above, should be subject to additional review prior to making a funding decision and throughout the course of the research, if funded. The working group has identified 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 the principles below before determining whether the proposal is suitable for funding. Studies that cannot be or are not anticipated to a high degree of confidence to be conducted in accord with the principles below should not be funded.

Principles for guiding review and funding decisions about research proposals anticipated to involve GOF studies of concern:

i. The research proposal has been evaluated by a peer-review process and determined to be scientifically meritorious and has been assessed to be likely to exert a sustained, powerful influence on the research field(s) involved.

ii. **An assessment of the overall potential risks and benefits associated with the project determines that the potential risks compared to the potential benefits are justified**. In general, the potential benefits associated with a research project should be commensurate with or exceed the presumed risks. Projects involving significant risks and few anticipated benefits should not be funded. If the potential risks appear high, the possible benefits should also be compelling. The justification for funding research with fewer risks would require less substantial benefits. Risks should be mitigated whenever possible.

iii. 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 a GOF study of concern. It is possible that the proposed GOF approach that raises concern is the only feasible approach for addressing the scientific question at hand. In other cases, modifications of the experimental design, selection of attenuated or other strains that pose

fewer risks in humans, or altogether different approaches that may provide the same or very similar information. Lines of experimentation that entail less risk should be pursued whenever possible.

iv. **The investigator and institution proposing the research have the demonstrated capacity to carry it out safely and securely.** Prior to funding, the risks associated with a proposed GOF study of concern must be identified and assessed, and plans should be developed to ensure that they are managed throughout the course of the work. Depending on the nature of the pathogen and the study in question, Gryphon's risk and benefit assessments may provide information about the risks associated with the study or the major drivers of risk for a particular manipulation. In order to manage risks associated with GOF studies of concern, an institution must have adequate resources, security, trained personnel, administrative structures, occupational health and safety procedures, and the ability to adapt to unanticipated results by increasing containment or adding safety or security features. In addition to minimal 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 embody the culture of responsibility as it pertains to safety and security, perhaps demonstrated through adherence to a code of conduct or other voluntary measures.

v. **The research information is anticipated to be broadly and legally shared in order to realize its potential benefits to global health.**

vi. **The research will be supported through funding mechanisms that include appropriate oversight of: a) all aspects of the research including its conduct, b) the sharing of data and materials, and c) the communication of the research.**

vii. **The proposed research is ethically justifiable.** Determinations about whether proposed GOF studies of concern should be undertaken will involve value judgments to assess the potential risks and benefits and determine 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 GOF studies of concern.

The NSABB working group has developed the following proposed conceptual approach for guiding funding decisions about GOF studies of concern. First, proposals involving potential GOF research of concern should be identified. The three characteristics above describing GOF studies of concern should guide these identifications. Next, studies identified as GOF studies of concern should be reviewed to determine whether funding and conducting the proposed study would be in line with the seven principles for guiding funding decisions. Only studies that are determined to be in line with these principles should be funded. Additional risk mitigation measures, including ongoing oversight measures, may be required in order for certain studies to be deemed acceptable for funding. Finally, studies that are funded should be conducted in accordance with all relevant policies, including periodic institutional and Federal review and monitoring, as well as any additional measures that were identified and stipulated.

Proposed Conceptual Approach for Funding Potential GOF Studies of Concern

1. Identify proposals anticipated to involve GOF studies of concern, as described by the following attributes:

i. The pathogen generated is highly transmissible in a relevant mammalian model

ii. The pathogen generated is significantly virulent in a relevant mammalian model, and

iii. The pathogen generated is likely resistant to control measures or more capable of being spread among human populations than currently circulating strains of the pathogen.

2. Review proposal to determine whether they meet the following criteria:

i. The research proposal has been evaluated by a peer-review process and determined to be scientifically meritorious and has been assessed to be likely to exert a sustained, powerful influence on the research field(s) involved.

ii. An assessment of the overall potential risks and benefits associated with the project determines that the potential risks compared to the potential benefits are justified.

iii. 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.

iv. The investigator and institution proposing the research have the demonstrated capacity to carry it out safely and securely.

v. The research information is anticipated to be broadly and legally shared in order to realize its potential benefits to global health.

vi. The research will be supported through funding mechanisms that include appropriate oversight of: a) all aspects of the research including its conduct, b) the sharing of data and materials, and c) the communication of the research.

vii. The proposed research is ethically justifiable.

Proposals not meeting these criteria should not be funded.

3. Fund, do not fund, or fund with required additional risk mitigation measures or stipulations.

4. Conduct the research in accordance with applicable oversight policies and employ any additional risk mitigation strategies that were identified at the time of funding or that are deemed necessary during the course of the research.

i. Research should be reviewed regularly at the institutional level

ii. Research should be reviewed regularly by the Federal funding agency

Figure 5. Proposed conceptual approach for guiding funding decisions for GOF studies of concern.

Recommendation 2. In general, oversight mechanisms for GOF studies of concern should be incorporated into existing policy frameworks. The risks associated with some GOF studies of concern can be identified and adequately managed by existing policy frameworks if those policies are implemented properly. However, the level of oversight provided by existing frameworks varies by pathogen. For some pathogens, existing oversight frameworks are robust and additional oversight mechanisms should generally not be required. For other pathogens, existing oversight frameworks are less robust and may require supplementation. All relevant policies should be implemented appropriately and enhanced when necessary to effectively manage risks.

All life science research involving pathogens entails risks; laboratory workers could be infected by a pathogen during the course of their work or a laboratory pathogen could be accidentally or intentionally released into the surrounding environment. There are numerous practices and procedures that are required of researchers and institutions conducting such work to manage these risks. The majority of GOF studies do not entail generating pathogens with pandemic potential and as such, the risks

associated with most studies are not novel or significantly concerning. Importantly, for risks to be adequately managed, policies must be implemented effectively at the Federal and institutional levels.

For GOF studies of concern, the working group recommends that any additional oversight be built into existing mechanisms. New policies or wholly new approaches are not necessary to manage the risks associated with these studies. There are precedents for additional Federal-level pre-funding review of certain GOF studies (i.e. *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 programs) 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 GOF studies of potential concern.

Not all GOF studies of concern would necessarily be subject to the entire suite of U.S. oversight policies. For instance, experimental manipulations with pathogens not included in the USG policies for DURC oversight or on the select agent list could still conceivably generate a pathogen that is highly transmissible, significantly virulent, and resistant to public health control measures. Additional oversight measures may need to be stipulated at the time of funding for proposals involving potential GOF studies of concern that are not subject to a particular policy that is deemed necessary. For instance, specific, enhanced containment practices may be required or a project may require ongoing monitoring for DURC potential at the Federal and institutional level.

In order to manage risks throughout the lifecycle of the research, potential risk mitigation features should be considered prior to funding GOF studies of concern. These might include:

- Additional training of researchers
- Enhanced biosafety practices or features, as dictated by the specific strains and proposed manipulations
- Enhanced security measures around strains, reagents, notebooks, and personnel
- An added requirement that the research be subject to the USG DURC policies, if it is not already
- More frequent institutional reviews of the research
- More frequent progress reports and discussions with Federal funding agency staff
- A requirement that the investigator and funding agency identify certain experimental outcomes that would trigger a re-evaluation of the risks and benefits prior to proceeding with a study
- A requirement for a responsible communication plan, specifically, including a description of biosafety and biosecurity practices
- A requirement that the institution be in regular communication with local law enforcement and/or public health officials
- A requirement for a bioethics consultation at the local and Federal level throughout the lifecycle of the research

Recommendation 3. The risk-benefit profile for GOF studies of concern may change over time and should be re-evaluated periodically to ensure that the risks associated with such research is adequately managed and the benefits are being realized.

An adaptive policy approach should be pursued to help ensure that oversight and risk mitigation measures remain commensurate with the risks associated with the research. An adaptive approach for GOF studies of concern would entail the continual evaluation of the risks and benefits associated with the research as well as the burdens and effectiveness of the proposal review process and ongoing risk 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 study may change if new countermeasures are developed or if new scientific or other information emerges to clarify certain risks or enable certain benefits. Importantly, such an approach would entail identifying at the outset the data or metrics that should be monitored and evaluated in order to inform policy efforts for GOF studies of concern.

Recommendation 4. The U.S. government should continue efforts to strengthen biosafety and biosecurity, which will foster a culture of responsibility that will support not only the safe conduct of GOF studies of concern but of all research involving pathogens.

Current discussions about GOF studies of concern are related to broader domestic and international discussions about laboratory safety and security. A "Top Down" approach to managing the risks associated with GOF studies of concern through Federal policies and oversight is appropriate. However, top-down policies and oversight alone will likely not be sufficient to fully address the associated risks. It is also critical to have safe and secure laboratory environments for conducting pathogen research, particularly certain GOF studies. It will also be important to facilitate a "Bottom Up" approach whereby scientific leaders and researchers involved in the design and conduct of GOF experiments are educated about biosafety, biosecurity, and the responsible conduct of their research. The goal should be to create a culture of responsibility, or "citizenship," whereby all participants in the research enterprise have a sense of shared responsibility for its continued beneficial contribution. Such a culture would value safety, security, and compliance, and work to promote public trust in the scientific enterprise. For GOF studies entailing significant risks a combination of voluntary and mandated oversight and risk mitigation measures would be beneficial. Institutional review and oversight may be adequate, but additional funding agency or other Federal-level review may be needed for certain situations.

7. Remaining Questions to Consider

As noted, the NSABB working group's analysis, findings, and potential recommendations are preliminary and may evolve pending further analysis and discussion with the Board and additional stakeholders. Here, the working group has identified a number of remaining questions and issues to consider. These and other questions will be explored at the January 2016 NSABB meeting. The working group also invites comments on the question below, or any aspect of this document, at nsabb@od.nih.gov.

1. How well does this working paper identify the GOF studies of greatest concern?

2. This working paper generally posits that the risks associated with GOF studies, including those involving the generation of certain pathogens with pandemic potential, can be adequately managed under current policy frameworks. Are there GOF studies that should require an additional level of review or oversight? If so, why? What should that oversight entail? Should that oversight occur at the federal or institutional level, or both? For what pathogens are current policy frameworks adequate to address GOF research? For what pathogens are current policy frameworks inadequate, requiring supplementation to address GOF research?

3. Are there GOF studies that should not be conducted? If so, which studies and why?

4. How well would the working group's description of GOF studies involving the generation of pathogens with pandemic potential and the principles for guiding review and funding decisions guide the review GOF studies that have raised concerns and inform decisions about whether to fund such studies?

5. Are there specific risk mitigation measures that should be required in order for certain GOF studies to be safely conducted?

6. How well does this working paper address ongoing oversight of GOF studies of concern? Are additional principles or oversight tools needed?

8. Appendices

Appendix A. Detailed 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 consisted of 13 NSABB voting members as well as non-voting *ex officio* members and other *ad hoc* members from Federal agencies. (Appendix A). 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, which was developed further based on input from all Board members, and ultimately approved by the full Board on May 5, 2015. 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. 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's framework describes: principles that should underpin the risk and benefit assessments; pathogens, pathogen characteristics, and types of GOF experiments and phenotypes that should be examined; the types of risks and benefits that should be analyzed; scenarios, conditions, and events to be examined; and approaches and methods that should be considered when analyzing risks and benefits. In order for the risk and benefit assessments to be grounded in scientific data and evidence, the assessments needed to focus on specific pathogens, experimental manipulations, and scenarios whose risks and benefits could be modeled and analyzed. The NSABB recommended that the risk and benefit assessments 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 risk and benefit assessments would provide

information specific to the pathogens and scenarios that were examined, but intended that the assessment would generate information that could be more broadly interpreted and applied. Thus, NSABB's recommended approach to the risk and benefit 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 beginning in June 2015 and remains active the time of this writing. The working group consists of 18 NSABB voting members as well as non-voting *ex officio* members and other *ad hoc* members from Federal agencies. (Appendix A). 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 risk and benefit assessments 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 Scientific conveying the results of the risk and benefit assessments, 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 5 times between October 2014 and January 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 D.

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.[45] On May 5, 2015, NSABB voted to approve its *Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research*.[46] This working paper was shared for discussion by the full NSABB on January 7 & 8, 2016.

Role of the National Academies in the Deliberative Process

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

[45] 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

[46] http://osp.od.nih.gov/sites/default/files/resources/NSABB_Framework_for_Risk_and_Benefit_Assessments_of_GOF_Research-APPROVED.pdf

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 conducting GOF studies that have raised concerns.[47] The discussions at this meeting directly informed the development of NSABB recommendations for conducting the risk and benefit assessments 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 Scientific. A common theme at this National Academies meeting was also 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 in its subsequent analysis of the risk and benefit assessments 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 to the NSABB to explore these topics, as well as ethical issues, further.

The second National Academies meeting will be held on March 10 & 11, 2016 and will include a discussion of the completed risk and benefit assessments and NSABB's preliminary findings and draft recommendations.

The Risk and Benefit Assessments of GOF Studies

NIH commissioned Gryphon Scientific to perform a 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 risk and benefit assessments, 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 risk and benefit assessments. In November 2015 the NSABB working group began receiving the results of the completed risk and benefit assessments. Gryphon's final draft report was posted in advance of the NSABB meeting in January, 2016.[48]

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

[47] 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.
[48] Risk and Benefit Analysis of Gain-of-Function Research, Final Draft Report. Gryphon Scientific, December, 2015. http://osp.od.nih.gov/sites/default/files/Risk%20and%20Benefit%20Analysis%20of%20Gain%20of%20Function%20Research%20-%20Draft%20Final%20Report.pdf

provided in the NSABB's *Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research* continued to inform the conduct of the risk and benefit assessments, 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 would yield 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 ethical input and analysis. NIH commissioned Professor 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 risk 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 risk-benefit analysis. 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 working group and posted in advance of the NSABB meeting in January, 2016. [49]

[49] Selgelid, Michael. Gain-of-Function Research: Ethical Analysis. December 7, 2015. http://osp.od.nih.gov/sites/default/files/GOF%20%20White%20Paper%20by%20Michael%20Selgelid_0.pdf

Appendix B. Summaries of Stakeholder Perspectives

In addressing its charge the NSABB consulted a wide range of experts and stakeholder groups. Such stakeholders include not only scientists and institutions that fund and conduct life sciences research, but a much larger and diverse array of groups including public health researchers, medical practitioners, emergency responders, vaccine developers, scientific journals, as well as the general public, non-governmental organizations, and others. To accomplish this, NSABB provided a variety of opportunities for interested groups and individuals to express their views and contribute throughout the deliberative process in ways that will inform the NSABB deliberations. These include: several full NSABB public advisory committee meetings with sessions dedicated to obtaining public comment, a public meeting hosted by the National Academies (and a second planned for March 2016) that obtained comments from the public at the meetings and online, as well as comments submitted to the NIH/OSP 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 recently on this topic. A complete list of the individuals consulted and articles examined by NSABB are listed in Appendix D. Note that Gryphon Scientific also conducted extensive consultations with experts as part of their risk and benefit assessments. Those experts are not listed here but available in Gryphon's report. [50]

The following is a synthesis of stakeholder ideas and opinions expressed during the deliberative process to date. 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 studiers also point out that such studies are needed for predicting what amino acid changes are important for transmission and therefore are important for the selection of candidate vaccine viruses. GOF studies are also important for prioritizing viruses for risk management (surveillance) and that further work will make these applications more robust.

[50] Risk and Benefit Analysis of Gain-of-Function Research, Final Draft Report. Gryphon Scientific, December, 2015. http://osp.od.nih.gov/sites/default/files/Risk%20and%20Benefit%20Analysis%20of%20Gain%20of%20Function%20Research%20-%20Draft%20Final%20Report.pdf

While acknowledging there are risks, 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 with appropriate containment along with good training and with the involvement of 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, virulence, 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, and GOF research is needed to develop animal models that will benefit development of countermeasures. 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 or transmissibility in mammals (particularly by the respiratory route), which results in the generation of a novel pathogen with pandemic potential. Some critics of GOF studies have acknowledged that there are a number of GOF studies that can and should be conducted. Critics have argued that the generation of novel laboratory pathogens with pandemic potential poses major public health risks, including the possibility of pandemics. They have presented and published calculations that suggest a strong probability of global outbreaks of influenza that might kill hundreds of millions of people, as a result of the release form 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.

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 stating that it is not possible to predict phenotype from genotype, therefore predicting the pandemic risk or newly emergent strains is not achievable given the current state of the 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, 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, and would be a better use of scarce resources. 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 of certain GOF studies have pointed out a moral issue if risks and benefits not fairly distributed globally.

Funding Agencies

Public and private funding agencies support the types of GOF research that has raised concern 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 have requirements and procedures in place to apply policies and guidance to funded work and to evaluate proposed work. Current approaches involve education and awareness campaigns, project evaluation, 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 clear guidance and workable policies 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 point because this does not cover privately funded research and research funded by other governmental entities. National 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 broadly and specifically 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. Solving one will not necessarily solve the other.

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 consequences of a deliberate release or determine how to prevent and/or mitigate one, and different experts view the probabilities and

consequences of potential biosecurity events 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 limitation, depending on one's perspective. Life sciences research that requires classification is typically "borne classified" and 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 several have in place 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 nor the access to such expertise to make the necessary judgments and decisions about risks associated with communicating 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 a national group such as the NSABB. 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 publication venues make controlling information increasingly difficult, and, as 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 for pathogens with pandemic potential 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, and with characteristics of strains that are likely to emerge in 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 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, 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

A number of participants stressed the importance of having meaningful public engagement with input and participation as part of the deliberative 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. The public opinion of science is harmed when decisions that influence public health and safety are made without such input. More than one participant raised the concern that if risks and benefits are not equitably distributed, it is a serious ethical issue[51]. It was also stressed that strong connections with state and local laboratories should be established for sharing information.

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. At the local level, they would welcome more guidance to help with decisions and provide clarification of existing policies and issues.

Foreign Scientists and Government Officials

Several 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 be doing at the end 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

[51] 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.

countries have well-developed systems of policy and regulation that would address 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 and benefit all. In addition, it was suggested that multi-national organizations such as WHO can play an important role. 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. The European Commission uses a comprehensive ethics process for screening and monitoring DURC/GOF in research projects.[52]

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 with decisions made by neutral parties. They want the final result of 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. Again, values were seen as very important, but it was noted some may be incompatible with one another. In addition, it was pointed out that regulation has costs and that oversight tends to lag behind scientific advances.

Both proponents and critics of GOF studies criticized the term “gain-of-function” as being too broad and not descriptive enough. Many criticized the funding pause for being too broad and some described it as too disruptive to the scientific process.

[52] The EU Framework Programme for Research and Innovation, Horizon 2020. 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 C. Consultations, Comments, and Sources Consulted During NSABB Deliberations

Table 1. Experts consulted by NSABB or the NSABB working groups (as of December 2015). Individuals listed here addressed the NSABB or NSABB working group in their individual or professional capacities. 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.	Public Comment
Richard Adams		Public Comment
Ronald Atlas, Ph.D.	University of Louisville	National Academies Workshop (December 15, 2014)
Ralph Baric, Ph.D.	University of North Carolina	National Academies Workshop (December 15, 2014), Public Comment
Kavita Berger, Ph.D.	Gryphon Scientific	NSABB Full Board Meeting (September 28, 2015)
Kenneth W. Bernard, M.D.	US Public Health Service (ret.)	Public Comment
Thomas Briese, Ph.D.	Columbia University	National Academies Workshop (December 15, 2014)
Arturo Casadevall, M.D., Ph.D.	Albert Einstein College of Medicine, mBio	NSABB Full Board Meeting (October 22, 2014), In-person WG Meeting (July 23, 2015), Public Comment
Rocco Casagrande, Ph.D.	Gryphon Scientific	NSABB Full Board Meeting (September 28, 2015)
R. Alta Charo, J.D.	University of Wisconsin–Madison	National Academies Workshop (December 15, 2014)
Susan Coller-Monarez, Ph.D.	Office of Science and Technology Policy	In-person WG Meeting (July 23, 2015)
Derrin Culp	White Plains, New York	Public Comment
Mark Denison, M.D.	Vanderbilt University	National Academies Workshop (December 15, 2014), Public Comment
Dennis Dixon, Ph.D.	HHS/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)
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.	Department of Homeland Security	In-person WG Meeting (July 23, 2015)
Stephen Eubank, Ph.D.	Virginia Polytechnic Institute and State University	NSABB Full Board Meeting (October 22, 2014)
Nicholas Evans, Ph.D.	University of Pennsylvania	Public Comment

David S. Fedson, M.D.	Sergy Haut, France	Public Comment
Scott Ferson, Ph.D.	Applied Biomathematics	NSABB Full Board Meeting (October 22, 2014), Public Comment
Harvey Fineberg M.D, Ph.D.	University of California, San Francisco	National Academies Workshop (December 15, 2014)
Baruch Fischhoff, Ph.D.	Carnegie Mellon University	NSABB Full Board Meeting (October 22, 2014); National Academies Workshop (December 15, 2014)
Ron Fouchier, Ph.D.	Erasmus Medical Center	National Academies Workshop (December 15, 2014), Public Comment
Gregory Frank, Ph.D.	Infectious Diseases Society of America	Public Comment
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)
Matt Frieman, Ph.D.	University of Maryland	Public Comment
Gigi Kwik Gronvall, Ph.D.	University of Pittsburgh Medical Center (UPMC) Center for Health Security	National Academies Workshop (December 15, 2014)
Charles Haas, Ph.D.	Drexel University	National Academies Workshop (December 15, 2014)
Peter Hale	Foundation for Vaccine Research	Public Comment
Elizabeth Hart	Adelaide, South Australia	Public Comment
Andrew M. Hebbeler, Ph.D.	White House Office of Science and Technology Policy	NSABB Full Board Meeting (October 22, 2014), National Academies Workshop (December 15, 2014)
Denise Hein		Public Comment
Gavin Huntley-Fenner, Ph.D.	Huntley-Fenner Advisors	National Academies Workshop (December 15, 2014)
Jo Husbands, Ph.D.	Board on Life Sciences of the US National Academy of Sciences	In-person WG Meeting (July 23, 2015)
Michael Imperiale, Ph.D.	University of Michigan	National Academies Workshop (December 15, 2014), Public Comment
Tom Inglesby M.D.	University of Pittsburgh	NSABB Full Board Meeting (October 22, 2014), Public Comment
Barbara Jasny, Ph.D.	Science	In-person WG Meeting (July 23, 2015)
Barbara Johnson, Ph.D., R.B.P.	Biosafety Biosecurity International	National Academies Workshop (December 15, 2014)
Laura Kahn, M.D., M.P.H., M.P.P.	Woodrow Wilson School of Public and International Affairs, Princeton University	Public Comment
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)
Yoshihiro Kawaoka, D.V.M., Ph.D.	University of Wisconsin, Madison	NSABB Full Board Meeting (October 22, 2014), National Academies Workshop (December 15, 2014), Public Comment
George Kemble, Ph.D.	3-V Biosciences	National Academies Workshop (December 15, 2014)
Larry Kerr, Ph.D.	National Security Council Staff	WG Meeting (November 5, 2015)
Andy Kilianski, Ph.D.	National Research Council Fellow at US Army	Public Comment

Lynn Klotz, Ph.D.	Center for Arms Control and Non-proliferation	Public Comment
Gregory Koblentz, Ph.D., M.P.P.	George Mason University	National Academies Workshop (December 15, 2014)
Todd Kuiken, Ph.D.	The 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.	HHS/National Institutes of Health	In-person WG Meeting (July 23, 2015)
Carol Linden, Ph.D.	HHS/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 Meeting (October 22, 2014), National Academies Workshop (December 15, 2014), Public Comment
Patricia Long, J.D., LL.M.	HHS/Office of Security and Strategic Information	In-person WG Meeting (July 24, 2015)
Nicole Lurie, M.D., M.S.P.H.	HHS/Assistant Secretary for Preparedness and Response	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)
Rebecca Moritz, M.S., C.B.S.P., S.M.(NRCM)	University of Wisconsin–Madison	National Academies Workshop (December 15, 2014)
Peter Murakami	Baltimore, Maryland	Public Comment
Kalyani Narasimhan, Ph.D.	Nature Publishing Group	In-person WG Meeting (July 23, 2015)
Daniel O'Connell	Albany, Oregon	Public Comment
Kimberly Orr, Ph.D.	US 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)
Megan Palmer, Ph.D.	Center for International Security and Cooperation, Stanford University	Public Comment
Christopher Park	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)
Dustin Phillips	Louisville, Kentucky	Public Comment
Stanley Plotkin, M.D.	University of Pennsylvania	Public Comment
David Relman, M.D.	Stanford University	National Academies Workshop (December 15, 2014)
David B. Resnik, J.D., Ph.D.	HHS/National Institutes of Health	NSABB Full Board Meeting (October 22, 2014)

Colin Russell, Ph.D.	University of Cambridge	National Academies Workshop (December 15, 2014)
Steven L. Salzberg, Ph.D.	Johns Hopkins University School of Medicine	Public Comment
Monica Schoch-Spana, Ph.D.	University of Pittsburgh Medical Center (UPMC) Center for Health Security	National Academies Workshop (December 15, 2014)
Stacey Schultz-Cherry, Ph.D.	St. Jude Children's Research Hospital	NSABB Full Board Meeting (October 22, 2014), National Academies Workshop (December 15, 2014)
Shannon Scott		Public Comment
Michael Selgelid, Ph.D.	Monash University	NSABB Full Board Meeting (September 28, 2015)
Billie Sellers		Public Comment
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)
Lone Simonsen, Ph.D.	George Washington University	Public Comment
Andrew Snyder-Beattie	Future of Humanity Institute, University of Oxford	Public Comment
Charles Stack, M.P.H.	University of Illinois at Chicago	Public Comment
John Steel, Ph.D.	Emory University	Public Comment
Kanta Subbarao, M.B.B.S., M.P.H.	HHS/National Institutes of Health	National Academies Workshop (December 15, 2014), Public Comment
Robert Temple, M.D.	Food and Drug Administration	In-person WG Meeting (July 23, 2015)
Eileen Thacker, D.V.M., Ph.D., DACVM	Department of Agriculture	In-person WG Meeting (July 23, 2015)
Kimball Ward		Public Comment
Robert Webster, Ph.D.	St. Jude Children's Research Hospital	National Academies Workshop (December 15, 2014)
Jerry Weir, Ph.D.	Food and Drug Administration	National Academies Workshop (December 15, 2014)
Robbin Weyant, Ph.D., R.B.P. (ABSA)	Center for Disease Control and Prevention	National Academies Workshop (December 15, 2014), In-person WG Meeting (July 23,2015)
Gary Whittaker, Ph.D.	Cornell University	Public Comment
Carrie Wolinetz, Ph.D.	HHS/National Institutes of Health	NSABB Full Board Meeting (May 5, 2015)
Infectious Diseases Society of America	Infectious Diseases Society of America	Public Comment

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Authors	Title
Baek, Y.H., et al., 2015	Profiling and Characterization of Influenza Virus N1 Strains Potentially Resistant to Multiple Neuraminidase Inhibitors
Boddie, C., et al., 2015	Assessing the bioweapons threat
Cambridge Working Group, 2014	Cambridge Working Group statement (July 2014)
Casadevall, A., and Imperiale, M.J., 2014	Risks and benefits of gain-of-function experiments with pathogens of pandemic potential, such as influenza virus: A call for a science-based discussion
Casadevall, A., et al., 2014	An epistemological perspective on the value of gain-of-function experiments involving pathogens with pandemic potential
Doshi, P., 2008	Trends in Recorded Influenza Mortality - United States 1900–2004
Duprex, P., and Casadevall, A., 2014	Falling down the Rabbit Hole: aTRIP Toward Lexiconic Precision in the "Gain-of-Function" Debate
Environmental Protection Agency Science Policy Council, 2000	Risk Characterization - EPA Science Policy Council Handbook
European Academies Science Advisory Council, 2015	Gain of function: experimental applications relating to potentially pandemic pathogens
European Center for Disease Prevention and Control, 2012	Risk Assessment: Laboratory-created A(H5N1) viruses transmissible between ferrets
Evans, N.G., 2013.	Great expectations - Ethics, avian flu and the value of progress
Evans, N.G., et al., 2015	The ethics of biosafety considerations in gain-of-function research resulting in the creation of potential pandemic pathogens
Fedson, D.S., and Opal, S.M., 2013	The controversy over H5N1 transmissibility research
Fedson, D.S., 2013	How Will Physicians Respond to the Next Influenza Pandemic?
Fouchier, R., et al., 2012	Preventing Pandemics - The fight over flu
Gronvall, G., 2013	H5N1: A case study for dual-use research
Gronvall, G., and Rozo, M., 2015	A Synopsis of Biological Safety and Security Arrangements
Guthrie, S., et al., 2013	Measuring Research - A guide to research evaluation frameworks and tools
Herfst, S., et al., 2012	Airborne transmission of influenza A/H5N1 virus between ferrets
Imai, M., et al., 2012	Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to reassortant H5 HA/H1N1 virus in ferrets
Imperiale, M.J., and Casadevall, A., 2015	A New Synthesis for Dual Use Research of Concern

Inglesby, T.V., and Relman, D.A., 2015	How likely is it that biological agents will be used deliberately to cause widespread harm?
Jaffe, H., et al., 2013	Extra oversight for H7N9 experiments
Linster, M., et al., 2014	Identification, characterization, and natural selection of mutations driving airborne transmission of A/H5N1 virus
Lipsitch, M., and Bloom, B.R., 2012	Rethinking Biosafety in research on potential pandemic pathogens
Lipsitch, M., and Galvani, A., 2014	Ethical alternatives to experiments with novel potential pandemic pathogens
Lipsitch, M., and Relman, D.A., 2015	New Game, New Rules - Limiting the Risks of Biological Engineering
Maines, T.R., et al., 2011	Effect of receptor binding domain mutations on receptor binding and transmissibility of avian influenza H5N1 viruses
Miller, M., and Palese, P., 2014	Peering into the crystal ball: Influenza pandemics and vaccine efficacy
National Research Council/Institute of Medicine, 2015	Potential Risks and Benefits of GOF Research – NRC/IOM Workshop Summary (Full Report)
Nature Editorial, 2014	A ripe time for gaining ground
NIH Blue Ribbon Panel Slide Presentation, 2008	Blue Ribbon Panel Scientific Subcommittee Teleconference slide presentation (May 2008)
Osterholm, M., and Relman, D., 2012	Creating mammalian-transmissible A/H5N1 influenza virus: Social contracts, prudence, and alternative perspectives
Palmer, M.J., et al., 2015	A more systematic approach to biological risk
Pascua, P.N., et al., 2012	Virulence and transmissibility of H1N2 influenza virus in ferrets imply the continuing threat of triple-reassortant swine viruses
Patterson, A., et al., 2013	A framework for decisions about research with HPAI H5N1 viruses
Patterson, A., et al., 2014	Biocontainment laboratory risk assessment: perspectives and considerations
Presidential Commission for the Study of Bioethical Issues, 2010	New Directions - The Ethics of Synthetic Biology and Emerging Technologies
Richard, M. et al., 2013	Limited airborne transmission of H7N9 influenza A virus between ferrets
Roberts, A., et al., 2007	A Mouse-Adapted SARS-Coronavirus Causes Disease and Mortality in BALB/c Mice
Rozell, D.J., 2015	Assessing and Managing the Risks of Potential Pandemic Pathogen Research
Rozo, M., and Gronvall, G., 2015	The Reemergent 1977 H1N1 Strain and the Gain-of-Function Debate
Russell, C., et al., 2012	The potential for respiratory droplet-transmissible A/H5N1 influenza virus to evolve in a mammalian host
Russell, C., et al., 2014	Improving pandemic influenza risk assessment
Schultz-Cherry, S., et al., 2014	Influenza Gain-of-Function Experiments: Their Role in Vaccine Virus Recommendation and Pandemic Preparedness

Scientific Management Review Board Report, 2014	Approaches to Assess the Value of NIH-Supported Research
Scientists for Science, 2014	Scientists for Science statement (July 2014)
Stern, P.C., and Fineberg, H.V., 1996	Understanding Risk - Informing Decisions in a Democratic Society
Sullivan, M., et al., 2013 (RMS White Paper)	Influenza Pandemic Risk - The Contribution of Laboratory Pathogens to Excess Mortality Risk
Sutton, T., et al., 2014	Airborne transmission of highly pathogenic H7N1 influenza virus in ferrets
Taubenberger, J., et al., 2012	Reconstruction on the 1918 influenza virus: Unexpected rewards from the past
Tharakaraman, K., et al., 2014	Structural determinants for naturally evolving H5N1 hemagglutinin to switch its receptor specificity
Trevan, T., 2015	Rethink Biosafety
Trock, S., et al., 2015	Development of Framework for Assessing Influenza Virus Pandemic Risk
USG (June 2013)	Biological Safety Guidance for Research with Risk Group 3 Influenza Viruses - Human H2N2, 1918 H1N1, and HPAI H5N1
USG (December 2009)	Biosafety in Microbiological and Biomedical Laboratories BMBL (5th Edition)
USG (September 2014)	Companion Guide to the USG Policies for Oversight of Life Sciences Dual Use Research of Concern
USG (February 2005)	Environmental Impact Statement For the Galveston National Laboratory for Biodefense and Emerging Infectious Diseases
USG (as of July 2015)	Federal Select Agents and Toxins List
USG (July 2012)	Final Supplementary Risk Assessment for the Boston University National Emerging Infectious Diseases Laboratories (NEIDL)
USG (August 2013)	HHS Funding Framework for HPAI H5N1 Studies
USG (February 2013)	NIH Guidelines for Research Involving Recombinant DNA Molecules - Amendment Notice. February 21, 2013
USG (November 2013)	NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules
USG (October 2014)	USG Gain-of-function GOF Deliberative Process and Funding Pause Statement
USG (September 2014)	USG Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern
USG (March 2012)	USG Policy for Oversight of Life Sciences Dual Use Research of Concern
Volkswagen Foundation and Max Plank Society, 2014	Dual Use Research on Microbes - Biosafety, Biosecurity, Responsibility - Hanover Symposium Summary Report
Watanabe, T., et al., 2014	Circulating Avian Influenza Viruses closely related to the 1918 virus have pandemic potential
Zhang, Y., et al., 2013	H5N1 hybrid viruses bearing 2009/H1N1 virus genes transmit in guinea pigs by respiratory droplet

1904 ## Appendix D. Policy Analysis Summary Table

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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 (ISATTAC)	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 concern. 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 Controls (as of July 2014) 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.

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Appendix E. NSABB Roster

National Science Advisory Board for Biosecurity (NSABB) Roster

[Ŧ] NSABB Working Group Co-chair
[†] NSABB Working Group on the Design and Conduct of Risk and Benefit Assessments of Gain-of-Function Studies
[‡] NSABB Working Group on Evaluating the Risks and Benefits of Gain-of-Function Studies
[*] NSABB Member, Retired

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Stanford University

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Bureau of Communicable Disease
New York City Dept. of Health and Mental Hygiene

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Plant Sciences
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University of Texas Medical Branch

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National Center for Infectious Diseases
Centers for Disease Control and Prevention

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Immunology and Molecular Genetics University
of California, Los Angeles

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Certificate Program
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Mailman School of Public Health
Columbia University

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Environmental and Occupational Health
Milken Institute School of Public Health
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Keystone Symposia on Molecular
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Veteran's Health Administration
Department of Veteran's Affairs

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National Institutes of Health

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Department of Defense

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Biological Issue Manager and Advisor to the Director
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Susan Coller Monarez, Ph.D.
Assistant Director, National Health Security and International Affairs
Office of Science and Technology Policy
Executive Office of the President

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Bureau of International Security and Nonproliferation
Department of State

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Deputy Assistant Secretary
Office of Policy and Planning
Office of the Assistant Secretary for Preparedness and Response
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Acting Director
National Homeland Security Research Center
Environmental Protection Agency

Michael W. Shaw, Ph.D.
Senior Advisor for Laboratory Science
Office of Infectious Diseases
Centers for Disease Control and Prevention

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Department of Energy

Edward H. You
Supervisory Special Agent
Biological Countermeasures Unit
FBI Weapons of Mass Destruction Directorate
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Robert T. Anderson, Ph.D.[‡]
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Office of Biological and Environmental Research
Department of Energy

Diane DiEuliis, Ph.D.[†‡]
Senior Research Fellow
National Defense University
Department of Defense

Dennis M. Dixon, Ph.D.[† ‡]
Branch Chief, Bacteriology and Mycology
National Institutes of Allergy and Infectious Diseases
National Institutes of Health

Meg Flanagan, Ph.D.[† ‡]
Microbiologist, Biological Policy Staff
Bureau of International Security and Nonproliferation
Department of State

Denise Gangadharan, Ph.D.[‡]
Associate Director for Science
Division of Select Agents and Toxins
Office of Public Health Preparedness and Response
Centers for Disease Control and Prevention

Wendy Hall, Ph.D.[† ‡]
Special Senior Advisor for Biological Threats
Office of Chemical, Biological, and Nuclear Policy
Department of Homeland Security

Teresa Hauguel, Ph.D.[† ‡]
Program Officer
National Institutes of Allergy and Infectious Diseases
National Institutes of Health

Richard Jaffe, Ph.D., M.T. (ASCP)[‡]
Director of the Division of Medical Countermeasures Strategy and Requirements
Office of the Assistant Secretary for Preparedness and Response
Department of Health and Human Services

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Bureau of Industry and Security
Department of Commerce

Betty Lee, Ph.D.[† ‡]
Bureau of Industry and Security
Department of Commerce

Kimberly Orr, D.V.M, Ph.D.[† ‡]
Bureau of Industry and Security
Department of Commerce

Diane Post, Ph.D.[† ‡]
Program Officer
Influenza Project Officer
Respiratory Diseases Branch
National Institutes of Allergy and Infectious Diseases
National Institutes of Health

David B. Resnik, J.D., Ph.D.[† ‡]
Bioethicist and IRB Chair
National Institute for Environmental Health Sciences
National Institutes of Health

Sharlene Weatherwax, Ph.D.[‡]
Associate Director of Science
For Biological and Environmental Research
Department of Energy