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

RECOMMENDATIONS OF THE NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

National Science Advisory Board for Biosecurity
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PREAMBLE

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

BACKGROUND AND INTRODUCTION

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

Recently, the phrase "gain-of-function (GOF) research" has come to describe certain studies that increase the ability of a pathogen to cause disease. This phrase achieved prominence after two groups published findings demonstrating that highly pathogenic avian influenza H5N1 viruses with a small number of engineered mutations became transmissible between mammals by respiratory droplets.[1,2] Such studies were undertaken to help define the fundamental nature of human-pathogen interactions, with the goal of enabling assessment of the pandemic potential of emerging infectious agents, informing public health and preparedness efforts, and furthering medical countermeasure development. However, such GOF studies may entail biosafety and biosecurity risks, and significant concerns have been raised about whether these studies generate information that could be misused to cause harm or whether the modified viruses could pose a pandemic threat if they were to be accidentally or intentionally released.

In 2012, a voluntary suspension of certain GOF studies involving highly pathogenic avian influenza H5N1 viruses was undertaken by the influenza research community.[3] 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.[4,5] The U.S. Department of Health and Human Services (HHS) developed a framework for guiding its funding decisions about projects that may generate highly pathogenic H5N1 viruses that are transmissible between mammals by respiratory droplets.[6] This funding framework was later expanded to include H7N9 influenza viruses as well.[7] Under this framework, HHS considers newly submitted research project proposals involving certain GOF studies for their scientific and public health merits as well as associated biosafety, biosecurity, and dual use risks. HHS also identifies appropriate risk mitigation measures that are required. Studies that are deemed acceptable for funding may then proceed in accordance with any agreed-upon risk mitigation measures.

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

[4] 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

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

[6] *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

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

Given the biosafety incidents in U.S. Federal laboratories during the summer of 2014 and renewed concerns regarding laboratory safety and biosecurity, the U.S. government (USG) determined that the risks and benefits of GOF research must be re-evaluated.[8] A robust and broad deliberative process that will result in the adoption of a new Federal GOF research policy (which will apply to research funded by U.S. agencies whether conducted in the U.S. or abroad) has been undertaken. While this process takes place, the USG has instituted a pause in the provision of new USG funding for certain GOF research involving influenza, Middle East Respiratory Syndrome coronavirus (MERS) or Severe Acute Respiratory Syndrome coronavirus (SARS) viruses—pathogens determined to have pandemic potential. Restrictions on new funding apply as follows:

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

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

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

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

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

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

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

While the funding pause and the RA and BA are limited to specific pathogens,[9] products of the RA and BA are intended to inform broader NSABB deliberations, which will involve recommendations on a conceptual approach to the evaluation of proposed GOF studies that may extend to other high-consequence pathogens. NSABB recommendations will inform the USG as it develops and adopts policies about whether certain types of GOF studies on high-consequence pathogens with pandemic potential should be supported and, if so, how such funding proposals should be evaluated.

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

THE CHARGE TO THE NSABB

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

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

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

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

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

THE NSABB'S PROCESS

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

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

Finally, an issue of central importance to the entire deliberative process is public trust in the scientific enterprise. A possible negative outcome associated with the GOF issue is the loss of public trust if a laboratory accident involving modified strains were to occur or if GOF research were intentionally misused to cause harm. Loss of public trust is a serious concern and its impact could be felt widely across the scientific community. The deliberative process should be conducted with an eye toward maintaining public trust in the scientific enterprise and oversight of scientific research. To help ensure public trust, and to ensure the NSABB's deliberations are informed by broad input and diverse perspectives, the NSABB seeks to maximize stakeholder input and public engagement during the deliberative process. Of note, the deliberative process includes public forums hosted by the National Academies that are intended to gather input and foster broad discussions by the scientific and other stakeholder communities. The first forum was held in December 2014;[10] a second will be held later in the process. Additionally, NSABB meetings are open to the public and the Board encourages attendees to provide comments, either verbally or in writing. The NSABB encourages comments and input at any time, which can be submitted by emailing NSABB@od.nih.gov.

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

RECOMMENDATIONS REGARDING THE DESIGN AND CONDUCT OF THE RA AND BA

Guiding Principles

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

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

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

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

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

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

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

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

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

Particular consideration must be given to issues of uncertainty[11] and sensitivity[12] in presenting results. Ranges and bounds should be used to reflect the level of confidence in the results.

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

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

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

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

Pathogens and Pathogen Characteristics

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

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

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

Pathogens recommended for inclusion in the RA and BA:

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

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

2. **SARS-CoV**

3. **MERS-CoV**

Pathogen characteristics recommended for consideration in the RA and BA:

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

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

2. Enhanced morbidity and mortality in appropriate animal models.

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

4. Evasion of existing natural or induced immunity.

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

Risk Categories

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

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

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

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

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

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

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

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

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

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

Benefit Categories

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

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

2. **Biosurveillance:** These benefits would include those relevant to the processes of gathering, integrating, analyzing, interpreting, and communicating essential information that might relate to disease activity and threats to human, animal, or plant health.[13] Specifically, the potential benefits of relevant GOF studies should be examined for benefits to:

    a. **Public Health Surveillance[14]:** How GOF research may contribute to efforts to improve public health by aiding detection and monitoring of pathogens in the real world, or help to better recognize or predict outbreaks in human populations, and inform decision-making.

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

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

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

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

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

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

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

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

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

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

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

Historical Perspectives from Analysis of Past Experiences

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

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

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

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

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

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

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

Scenarios and Events to be Included in the RA

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

Development and Selection of Events and Scenarios

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

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

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

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

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

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

Categories of Events and Scenarios

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

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

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

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

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

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

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

7. Scenarios involving the escape of an infected animal

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

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

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

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

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

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

14. Scenarios based on alternative experimental approaches to GOF research

Types of Experiments in RA

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

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

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

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

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

4. Selection for drug-resistant mutants

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

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

Biosafety Assumptions for the RA

In order to assess the risks associated with GOF experiments it is necessary to define the biosafety level (BSL) and other related conditions under which the work may take place because differences in working conditions may significantly affect the risk of an experiment and possible adverse results. In the United States, the *Biosafety in Microbiological and Biomedical Laboratories* and the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*)[15] provide biosafety guidance regarding the conduct of risk assessments, and determination of appropriate laboratory practices and physical containment for research conducted with specific agents. These guidelines apply to certain Federally-funded research conducted in the U.S. and abroad and are frequently used by non-Federally-funded institutions and other countries as the model for biosafety guidance. The NSABB recommends that the contractor carefully examine current guidance for biocontainment, biosafety practices, training, and occupational health plans and incorporate these features into their analysis.

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

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

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

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

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

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

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

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

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

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

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

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

Appendix A

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

CHARTER

NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY

AUTHORITY

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

OBJECTIVES AND SCOPE OF ACTIVITIES

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

DESCRIPTION OF DUTIES

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

- Recommend strategies and guidance for enhancing personnel reliability among individuals with access to biological select agents and toxins.
- Provide recommendations on the development of programs for outreach, education and training in dual use research issues for scientists, laboratory workers, students, and trainees in relevant disciplines.
- Advise on policies governing publication, public communication, and dissemination of dual use research methodologies and results.
- Recommend strategies for fostering international engagement on dual use biological research issues.
- Advise on the development, utilization and promotion of codes of conduct to interdisciplinary life scientists, and relevant professional groups.

- Advise on policies regarding the conduct, communication, and oversight of dual use research and research results, as requested.
- Advise on the Federal Select Agent Program, as requested.
- Address any other issues as directed by the Secretary of HHS.

AGENCY OR OFFICIAL TO WHOM THE COMMITTEE REPORTS

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

SUPPORT

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

ESTIMATED ANNUAL OPERATING COSTS AND STAFF YEARS

The estimated annual cost for operating the Committee, including compensation and travel expenses for members, but excluding staff support, is $186,416. The estimated annual person-years of staff support required is 1.2 at an estimated cost of $178,705.

DESIGNATED FEDERAL OFFICER

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

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

ESTIMATED NUMBER AND FREQUENCY OF MEETINGS

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

DURATION

Continuing.

TERMINATION

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

MEMBERSHIP AND DESIGNATION

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

Areas of expertise to be represented on the NSABB, may include but are not be limited to:

- Molecular Biology/Genomics
- Microbiology (Bacteriology)
- Microbiology (Virology)
- Clinical Infectious Diseases/Diagnostics
- Laboratory Biosafety and Biosecurity
- Public Health/Epidemiology
- Health Physicist/Radiation Safety
- Pharmaceutical Production
- Veterinary Medicine
- Plant Health
- Food Production
- Bioethics
- National Security
- Military Biodefense Programs and Military Medicine
- Intelligence
- Biodefense
- Law
- Law Enforcement
- Academia
- Scientific Publishing
- Industry Perspective
- NIH Recombinant DNA Advisory Committee Experience/Perspective
- Public Perspective
- IBC perspective
- Export Controls

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

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

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

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

SUBCOMMITTEES

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

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

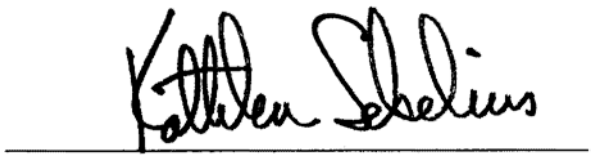
RECORDKEEPING

Meetings of the Committee and its subcommittees will be conducted according to the Federal Advisory Committee Act, other applicable laws and Department policies.
Committee and subcommittee records will be handled in accordance with General Records Schedule 26, Item 2 or other approved agency records disposition schedule. These records will be available for public inspection and copying, subject to the Freedom of Information Act, 5 U.S.C. 552.

FILING DATE

April 7, 2014

APPROVED



MAR 2 1 2014
Date

Kathleen Sebelius

Appendix B

National Science Advisory Board for Biosecurity
Roster

(*) Denotes members of the NSABB working group that developed the draft Framework for Conducting Risk and Benefit Assessments for Gain-of-Function Research

(#) Denotes co-chairs of the NSABB working group

NSABB Voting Members

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Office of the President
Stony Brook University

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President, Battelle National Biodefense Institute, LLC

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