National Institutes of Health (NIH)
Office of the Director
Office of Science Policy
Office of Biotechnology Activities
NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY (NSABB)

May 5, 2015
NIH Campus
9000 Rockville Pike
Building 31, Floor 6C, Room 10
Bethesda, MD

MEETING MINUTES

VOTING MEMBERS

Samuel L. Stanley, Jr., M.D., Chair
Kenneth I. Berns, M.D., Ph.D.
Craig Cameron, Ph.D.
Andrew Endy, Ph.D.
Christine M. Grant, J.D., M.B.A.
Marie-Louise Hammarskjöld, M.D., Ph.D.
Clifford W. Houston, Ph.D.
Joseph Kanabrocki, Ph.D., C.B.S.P.
Marcelle C. Layton, M.D.
James W. LeDuc, Ph.D.
Margie D. Lee, D.V.M., Ph.D.
Francis L. Macrina, Ph.D.
Joseph E. McDade, Ph.D. (participating via teleconference)
Jeffrey F. Miller, Ph.D.
Stephen S. Morse, Ph.D.
Jean L. Patterson, Ph.D.
I. Gary Resnick, Ph.D.
Susan M. Wolf, J.D.

AD HOC MEMBERS[1]

Theresa M. Koehler, Ph.D.

ABSENT

J. Patrick Fitch, Ph.D.
Jan Leach, Ph.D.
Rebecca T. Parkin, Ph.D.
David L. Woodland, Ph.D.

[1] *Ad hoc* members are incoming members who will participate in a non-voting capacity until their appointments to the Board are finalized.

***EX OFFICIOS* / FEDERAL AGENCY REPRESENTATIVES**
Todd Anderson, Ph.D., U.S. Department of Energy
Diane DiEuliis, Ph.D., U.S. Department of Health and Human Services
Dennis M. Dixon, Ph.D., National Institutes of Health
Gerald Epstein, Ph.D., U.S. Department of Homeland Security
M. Camille Harris, D.V.M., Ph.D., M.S., U.S. Geological Survey
David R. Liskowsky, Ph.D., National Aeronautics and Space Administration
Christopher J. Park, U.S. Department of State
Michael W. Shaw, Ph.D., Centers for Disease Control and Prevention
Edward H. You, Federal Bureau of Investigation

Welcome
Samuel L. Stanley, Jr., M.D., NSABB Chair
President, Stony Brook University

Dr. Stanley opened the meeting at 8:27 a.m. He welcomed the NSABB members in attendance and on the telephone, as well as other meeting participants, and said he was looking forward to an interesting and productive meeting.

He began by noting that Mary Groesch, Ph.D., and Amy Patterson, M.D., who had managed the efforts of the NSABB since it began, have taken on new positions in the National Heart, Lung, and Blood Institute. Dr. Stanley thanked them in absentia for their contributions and wished them the best in their future endeavors.

Dr. Stanley reintroduced Christopher J. Viggiani, Ph.D., acting director of the NSABB, and welcomed Carrie D. Wolinetz, Ph.D., the new associate director for science policy at the NIH.

On October 17, 2014, the U.S. government announced its decision to re-evaluate the risks and benefits associated with certain gain-of-function (GOF) studies involving pathogens with pandemic potential. Dr. Stanley explained that these studies are generally conducted to help better understand host-pathogen interactions and inform public health preparedness efforts. However, some GOF studies have raised concerns over whether a virus with enhanced transmissibility or pathogenicity could accidentally or intentionally be released from a laboratory. The government's announcement set forth a deliberative process involving the NSABB, the National Academies of Science, and the commissioning of a formal risk-benefit assessment (RBA) for GOF studies.

During the October 22, 2014, meeting, the Board was issued its charge, with two tasks and two deliverables. The first task is to provide advice on the design and conduct of the RBA, which will be conducted by Gryphon Scientific. This meeting would be focused largely on the first deliverable: a draft framework for the RBA. Dr. Stanley emphasized that the assessments alone will not address whether a certain study should or should not be performed, but that the information they yield will be taken into consideration as the NSABB crafts its second deliverable: recommendations on how the government should evaluate research proposals involving certain GOF studies. Dr. Stanley said that, to date, the Board has been focused on

developing guidance for the RBA. Once the draft framework is approved, the NSABB will turn its attention to the second deliverable.

Dr. Stanley summarized the agenda for the day's meeting, which included two public comment sessions. He acknowledged that the one-year timeline for deliberations proposed in the October 17 announcement was very ambitious—possibly too ambitious. However, the NSABB has made progress in the last six months:

- The NSABB has held two public meetings to discuss GOF research.
- The Board has issued a statement conveying concerns about the funding pause. This statement prompted the government to clarify its guidance.
- Many NSABB members attended a symposium on the subject at the National Academies of Science.
- The NSABB working group has drafted a framework to guide the design of the RBA.
- Gryphon Scientific has been selected and is ready to begin the RBA.

Dr. Stanley encouraged NSABB members to be mindful that certain research projects will remain paused as they deliberate. He said that they owe it to the scientific community to address their tasks rapidly and efficiently and to provide clarity in an environment of uncertainty.

Introduction of NSABB Voting and *Ex Officio* Members
Christopher J. Viggiani, Ph.D., Acting Executive Director, NSABB
Office of Science Policy, Office of the Director, NIH

Dr. Viggiani invited Board members and *ex officio* members to introduce themselves.

Review of Conflict-of-Interest Rules
Christopher J. Viggiani, Ph.D.

Dr. Viggiani explained that members of the NSABB are considered special government employees and as such are subject to federal rules of ethical conduct. He then reviewed the process for assessing and managing potential conflicts of interest.

Approval of NSABB Meeting Minutes
Samuel L. Stanley, Jr., M.D.

The meeting minutes from the October and November 2014 meetings were reviewed and unanimously approved without further edits.

Review of Gain-of-Function Deliberative Process and Charge to NSABB
Carrie D. Wolinetz, Ph.D., Associate Director for Science Policy, NIH

Dr. Wolinetz provided an overview of the deliberative process and the NSABB's role in the process. She emphasized that, while the term GOF is used as shorthand, the NSABB's eventual recommendations only concern a subset of GOF studies—those proposing to increase

pathogenicity or transmissibility in an agent with pandemic potential. She said that it was important to keep in mind why scientists perform GOF studies in the first place: to help define the fundamental nature of human-pathogen interactions. These studies therefore have the potential to:

- Enable assessment of the pandemic potential of emerging infectious agents
- Inform public health and preparedness efforts
- Further the development of medical countermeasures

She noted that GOF studies, particularly the subset in question, do present a dual-use dilemma. There are risks associated with this legitimate research: accidental or deliberate release of pathogens into the environment, as well as the misuse of information generated by research that could be used in a way to cause harm and pose a threat to public health or national security. It is the role of the NSABB to weigh these risks against the potential benefits.

Concern about the risks of GOF studies increased following the publication of two scientific studies on H5N1 influenza viruses, which were modified to be transmissible among mammals (ferrets) and recent biosafety incidents. As a result, the government announced a pause in certain GOF experiments involving high-risk pathogens—Middle East respiratory syndrome corona virus (MERS Co-V), severe acute respiratory syndrome corona virus (SARS Co-V), and influenza virus.

Dr. Wolinetz said that the NSABB is the locus of the deliberative process. She reiterated the work that the NSABB has done to date and noted that the National Academies of Science will be re-engaged in early 2016 to discuss the NSABB's draft recommendations. Dr. Wolinetz reviewed the NSABB's two primary responsibilities in this process.

Charge and Deliverable 1: Advise and provide a framework on the design, development, and conduct of the RBA.

Charge and Deliverable 2: Provide formal recommendations to the U.S. government on a conceptual approach to evaluating proposed GOF studies.

Dr. Wolinetz said that the NSABB's process will be dynamic and interactive. The NSABB working group will continue to engage with Gryphon Scientific as the RBA proceeds. Simultaneously, the NSABB will redirect its focus to Deliverable 2. The results of the RBA will feed into final policy recommendations. Dr. Wolinetz added that NIH staff members will be the liaisons between these two tracks. After the National Academies of Science public forum to discuss the draft recommendations, the NSABB will finalize and deliver its recommendations to the U.S. government. By mid-2016, the government's policy process will begin, leading eventually to a policy for assessing GOF studies and their funding in the future.

Update from the NSABB Working Group: Proposed Framework for the Conduct of Risk and Benefit Assessments on Gain-of-Function Studies Involving Pathogens with Pandemic Potential

Joseph Kanabrocki, Ph.D., C.B.S.P., Co-chair, NSABB Working Group
Associate Vice President for Research Safety, Professor of Microbiology, University of Chicago

Dr. Kanabrocki presented an overview of the working group's draft framework. He restated the charges given to the NSABB and said that the overall aim of the framework is to provide guidance to the NIH, who will be directing Gryphon Scientific in conducting the RBA. In order for the RBA to be credible, it should be grounded in data and the phenotypes associated with specific agents. However, one of the group's goals was to generate an RBA that would produce generalizable information that could be applied to future situations.

Dr. Kanabrocki said the working group was composed of 13 NSABB members, who offered expertise from medicine, infectious diseases, ethics, public policy, biosafety, law, and other areas. The NSABB members were joined by a number of federal representatives, who provided a similar breadth of diverse perspectives.

The working group has convened regularly via teleconference and had one in-person, one-day meeting at the NIH. During these discussions, the group sought to identify principles that should underpin the contractors' work and elements and considerations that should be factored into the studies. The group considered the discussion held during prior public meetings, relevant reading and background materials, and presentations from subject matter experts in several areas, including biosafety.

Dr. Kanabrocki outlined the major elements of the draft framework. He emphasized that the inclusion of particular pathogens or types of experiments is not intended to condemn or condone them. The goal was simply to get a broad sense of the risks and benefits of GOF studies to inform the committee's future deliberations.

Guiding Principles

The working group identified 12 guiding principles that should underpin the RBA:

1. The potential risks and benefits associated with certain GOF research should be formally and rigorously identified and analyzed.
2. The relative risks and benefits of alternative approaches to GOF studies should also be identified and analyzed.
3. The RBA should be designed to provide information that is useful for guiding NSABB recommendations.
4. The scope of the RBA must be sufficiently comprehensive but also appropriately focused on the subset of GOF studies with the most significant risk.
5. The RBA should be thoroughly documented and strive for clarity, transparency, consistency, and reasonableness.
6. The RBA should be objective, scientifically rigorous, and utilize peer-accepted methods, including quantitative and qualitative approaches.
7. The RBA should consider the effects of risk mitigation practices, public health interventions, and countermeasure effectiveness, as well as human error.
8. The RBA should rely on data wherever possible and acknowledge data sources, limitations, and assumptions, paying particular attention to issues of uncertainty and sensitivity in the presentation of results.
9. Examination of positive and negative outcomes that may result from conducting GOF research should include consideration of probability of occurrence, magnitude of effects, and realistic timeframes.

10. The RBA should focus on GOF studies in the United States, or supported by U.S. funding and conducted internationally, but also account for the fact that laboratories not funded by the United States may conduct similar studies.
11. Efforts should be made to express risks and benefits in the same terms when possible, while noting that benefits should not be limited to the reduction of risks.
12. The RBA should include scenarios to analyze a range of risks and include both intentional and accidental events.

Pathogens of Concern

Next, the working group identified three pathogens to include in the RBA: SARS Co-V, MERS Co-V, and three forms of influenza virus: seasonal, H5N1, and H7N9. Members felt it was especially important to include these agents because they were subject to the pause in funding and because viruses transmitted by respiratory droplets have great pandemic potential. Dr. Kanabrocki noted that the working group had not reached a final consensus on which other pathogens to include, if any, and solicited feedback from the full NSABB.

Pathogen Characteristics of Concern

The working group identified four characteristics of pathogens that raise particular concern:

- Enhanced virus production as a result of changes in any step of the virus replication cycle
- Enhanced morbidity and mortality in appropriate animal models
- Enhanced transmission in mammals (e.g., increased host/tissue range, altered route of transmission)
- Evasion of existing natural or induced immunity or evasion of the effects of countermeasures

Risk Categories

The working group identified six categories of risk that should be considered in developing the RBA due to their direct or indirect potential to adversely impact human or animal health:

- Biosafety, including laboratory accidents and exposure events
- Biosecurity, including breaches of physical and personnel security
- Proliferation, including the change in risk if more laboratories perform GOF research
- Information resulting from GOF studies that could be used for malevolent purposes
- Agricultural, including risks to food production
- Economic

Benefit Categories

The working group identified five categories of benefits that should be considered in the RBA due to their direct or indirect potential to positively impact human or animal health:

- Scientific knowledge
- Biosurveillance of public health, agriculture and companion animals, and wildlife
- Countermeasure development
- Informing policy decisions
- Economic benefits

Historical Perspectives

To aid in the consideration of the relative risks and benefits posed by GOF studies, the working group recommends analysis of existing historical data on the disease burden associated with the pathogens recommended for inclusion. This analysis should include:

- Analysis of global morbidity and mortality data associated with seasonal influenza, pandemic influenza, SARS, and MERS, and trends in these data over time
- Comparison of the morbidity and mortality associated with seasonal and pandemic influenza
- Analysis of the impact of influenza on food production
- Descriptions of how the data utilized were collected, interpreted, and analyzed
- Qualitative review of the impact of vaccines and therapeutics on pathogen-associated morbidity and mortality

Scenarios and Events

The risk assessment will involve analyzing and modeling the risks associated with various events that might be associated with GOF studies. For instance, one might analyze the likelihood that a specific laboratory accident occurs and then model the potential consequences that accident could have on laboratory workers and the surrounding community. The working group identified five principles that should guide the development of these scenarios:

- Scenarios and events should be scientifically, politically, and socially accurate and credible.
- To the extent possible, events and scenarios should be realistic and based on actual examples.
- The overall range of scenarios should encompass high- and low-risk events, high- and low-probability events, and highly unlikely but still credible events.
- The scenarios should involve events that are of concern to stakeholders, including the public, and include scenarios that involve experimental manipulations that ultimately may be determined to be prohibited under any circumstances.
- Scenarios involving security threats should be plausible but not necessarily based on specific, real-life examples and consider prior actions or expressed intent, current and reasonably achievable technical capabilities, and how readily security threats could be achieved or enabled by a certain type of GOF study.

The working group also identified types of events to consider when developing scenarios for the RBA:

- Laboratory accidents
- Substandard biosafety practices
- Accidental and deliberate release
- Natural disasters
- Escape of infected animals
- Security failures and breaches (insider and external threats)
- Alternative approaches to GOF studies

Types of Experiments

The working group identified six types of experiments that should be built into the RBA scenarios. These experiments may be reasonably expected to result in the generation of pathogens with enhanced pathogenicity and/or transmissibility in mammals:

- Passage in animals with the intent to alter host range and generate mammalian adapted strains or to develop an animal model of disease
- Genetic modifications or selection for traits that may increase pathogenicity or transmissibility
- Manipulations resulting in better growth or enhanced replication, for example, to make a vaccine strain
- Selection for antiviral resistant mutants
- Antigenic escape studies, that is, selecting for viruses that are not neutralized by certain antibodies
- Alternative experiments to GOF studies that may yield similar scientific information

Dr. Kanabrocki said that inclusion of these experiment types does not imply that all these studies are subject to the funding pause; they are simply the types of experiments that have been performed for legitimate purposes but could generate strains with concerning phenotypes.

Biosafety Assumptions

The working group recommends that existing domestic and international biosafety guidance and biocontainment capabilities be investigated and considered. For each pathogen, the RBA should analyze risks associated with multiple biosafety levels (BSL) so the effects of each level of mitigation can be determined. The RBA should also determine the effects of adequate or inadequate occupational medicine, training, standard operating procedures, and administrative controls.

Approaches and Methods

The final section of the framework describes a number of methods and approaches that the contractor should explore to assess the potential risks and benefits associated with GOF studies:

- Literature reviews and examination of knowledge indicators (e.g., science citation index), including consideration of quality and impact of information on the field
- Examination of commercialization indicators (e.g., number of patents), including considerations for quality and utility
- Interviews and consultations with a broad range of relevant U.S. and international experts about risks and benefits associated with GOF studies
- Development of illustrative case studies or descriptions where a GOF study has resulted in a specific risk or benefit
- Quantitative approaches to modeling the risks and benefits, particularly the risks and benefits to public health
- Quantitative approaches to modeling economic benefits and risks
- Development of "event trees" illustrating processes leading to tangible events that could result from GOF studies

Dr. Kanabrocki concluded his presentation by saying that the overall goal was to develop an RBA with an appropriate scope to examine thoroughly the risks and benefits associated with GOF studies of concern. However, the working group also tried to develop a framework that would provide generalizable information to inform future deliberations.

NSABB Review and Discussion of the Draft Framework for Conducting Risk and Benefit Assessments on Gain-of-Function Research
Kenneth I. Berns, M.D., Ph.D., Co-chair, NSABB Working Group
Distinguished Professor, Department of Molecular Genetics and Microbiology, Genetics Institute, College of Medicine, University of Florida

Dr. Berns invited the NSABB to discuss the proposed framework. He reminded the Board that the framework is a draft. Dr. Berns said that the working group would welcome feedback on any section but that input would be particularly appreciated on the following sections:

- Pathogens and pathogen characteristics
- Risk categories
- Benefit categories
- Scenarios
- Biosafety assessments

Pathogens
Dr. Berns noted that selecting which pathogens to include in the RBA was one of the greatest challenges for the working group. They agreed on the three pathogens included in the government moratorium, and that influenza viruses as a class should be considered rather than limiting the assessments to H5N1. He acknowledged that even three pathogens is a lot to include in the given timeline but that the working group wondered whether it might be worthwhile to include additional viruses to provide a more complete picture of GOF research risks and benefits.

James W. LeDuc, Ph.D., agreed with the three included agents but noted that the universe of pathogens is very large. He suggested emphasizing pathogen characteristics rather than specific pathogens. Dr. Berns agreed but noted that the contractors must have specific examples to incorporate concrete data into the RBA.

Susan M. Wolf, J.D., said that the working group's thought process was best captured by the following statement in the draft framework: "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."

Ms. Wolf read a sentence from the original charge to the NSABB: "Although GOF studies that fall within the scope of the pause will be a starting point for deliberations, the suitability of other types of GOF studies will be discussed." Ms. Wolf said that this suggests that the pathogens included in the funding moratorium are not the entirety of what should be considered as the NSABB formulates its final recommendations to the U.S. government. For now, the question is whether focusing the RBA on these three pathogens is adequate. She asked whether those pathogens are representative or whether additional agents should be included.

Stephen S. Morse, Ph.D., agreed that the question was difficult, but said he believed that the selected pathogens would make for good case studies. The focus should be on conclusions that can be generalized, as new agents of concern are sure to arise in the future.

Jeffrey F. Miller, Ph.D., asked whether there are relevant characteristics of pathogens that might not be represented by the three selected pathogens.

Craig E. Cameron, Ph.D., asked why bacterial pathogens were excluded from the deliberations. Dr. Berns said that they had been discussed but that the major pandemics of the last century have been viral in nature.

Dr. Stanley said that there is universal agreement that the three agents selected by the working group are important to include, but should additional needs make themselves known, the NSABB would like to have the opportunity to add additional pathogens to the RBA as the work proceeds.

Dr. Berns agreed that the RBA is meant to be a dynamic project and that the working group will continue to collaborate with Gryphon Scientific to ensure that the RBA meets the NSABB's needs.

Dr. Viggiani asked whether a Gryphon Scientific representative could confirm the flexibility of the process. He asked whether it would be possible for the NSABB to choose to add an agent or make modifications once the work has begun.

Mark Kazmierczak, Ph.D., a senior analyst at Gryphon Scientific, responded that everything discussed so far was agreeable with Gryphon's intended approach to the RBA. He said that the RBA will focus on characteristics of pathogens and benchmarking that information against pathogens of interest. If the NSABB working group elects to include additional pathogens that will not be a problem, as the process is designed to be dynamic.

Pathogen Characteristics

Dr. Berns reiterated the four characteristics of concern and asked the NSABB for comment.

Francis L. Macrina, Ph.D., said that one way to test the generalizability of the selected characteristics was to examine how each characteristic could be adjusted to cover a vast array of infectious agents. Dr. Macrina noted that the draft framework separates antiviral-resistant mutations from antigen escape studies. He suggested combining those two experiment types into a single item and adding drug resistance as a new bullet point. Dr. Berns supported this suggestion.

Clifford W. Houston, Ph.D., asked why airborne bacteria were not included in the pathogen characteristics. Dr. Berns responded that the working group intended the phrase "altered or enhanced transmission or route of transmission" to encompass all airborne microorganisms, but he acknowledged that the current language may be too vague.

Dr. Stanley said that Dr. Houston was trying to ensure that the framework uses broad enough language to capture bacteria as well as viruses.

Dr. LeDuc reiterated his belief that the NSABB should be focusing more on pathogen characteristics than on specific pathogens because these underlying principles will form the basis for legislation and policy. Dr. Stanley responded that determining guiding principles falls more under the domain of Deliverable 2 and that the NSABB's current task is to determine what information is relevant to incorporate into the RBA to yield information that will best inform those recommendations.

Ms. Wolf said she agreed that it was important to keep bacterial agents in mind. She recommended replacing the word "virus" with "pathogen" in the framework document.

Theresa M. Koehler, Ph.D., suggested that "enhanced virus production" similarly be changed to "microorganism" or another general term. Dr. Berns concurred.

Marcelle C. Layton, M.D., asked whether "enhanced transmission in mammals" should be made more explicit, since the NSABB seemed to be discussing primarily transmission via aerosol or respiratory routes. Dr. Berns said that while that was true for the three included agents, the working group wanted the framework document to be more generalizable to modes of transmission for other pathogens as well. Dr. Miller concurred, saying that the Ebola virus was transmitted primarily by contact but was still extremely efficient.

Dr. Viggiani summarized the two edits recommended in the discussion so far:

- Reword the language of pathogen characteristics to describe pathogens, not viruses.
- Add a fifth pathogen characteristic: evasion of the effects of medical countermeasures.

Risk Categories

Dr. Berns reiterated the six proposed risk categories: biosafety, biosecurity, proliferation, informational, agricultural, and economic. He noted that biosafety issues affect the risk of loss of public confidence in the scientific enterprise. If there is evidence of imperfect biosafety, public support for GOF research could drastically decrease.

Dr. Berns said that biosecurity is a real-world consideration when working with highly dangerous pathogens. One question to consider is whether any of the included agents could be attractive to bioterrorists.

Dr. Berns said proliferation is another real issue and one that the United States cannot control. He said that smaller "garage-based" laboratories exist and often do not adhere to standard BSL guidelines. GOF research happens all over the world, including in countries that may not have as strict regulations in place. At present, there is no effective international mechanism for extending U.S. mandates to research performed in other countries. For this reason, it is vital to engage in discussion with policymakers and researcher institutions in other nations.

Dr. Kanabrocki said that the RBA will model the conditions under which these studies are performed, both in the United States and abroad.

Dr. Berns mentioned the *Biosafety in Microbiological and Biomedical Laboratories* manual, which provides containment guidelines for researchers working with various agents.

Dr. LeDuc agreed that since GOF research is also conducted outside the US, international engagement is very important. He encouraged the NSABB to pursue international discussion and collaboration.

Dr. Berns noted that the Biological and Toxin Weapons Convention has no associated inspection regime and is a purely voluntary agreement that has been violated in the past by major players.

Ms. Wolf noted that concerns about the risks of international GOF research do appear twice in the draft framework. The first appears on lines 44 and 46, where the document states, "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." The second mention addresses the risks of proliferation.

Dr. Berns said that information risk is essentially a dual-use research of concern (DURC) issue and is best evidenced by the discussion around the two H5N1 journal articles published in 2012. It will be challenging to calculate the risks associated with open publication, and much of the responsibility falls on the editors of scientific journals. Historically, very few papers have been rejected for DURC considerations. The working group agreed that it would be challenging for the U.S. government to forbid the publication of results of research it had funded. In some cases, publication is a condition of collaboration with other countries. Restricting the release of findings could have international implications.

Gary Resnick, Ph.D., said that different federal funding organizations have different approaches to managing the release of information and that this is an opportunity to mitigate risks. He suggested incorporating this concept into the NSABB's eventual policy recommendations. Dr. Berns noted that some government agencies fund classified research while others, like the NIH, do not, and this distinction may explain the diversity in publication policies.

Dr. Berns pointed out that the definition of DURC includes consideration of the effects on agriculture and environment, and the working group felt it was important to consider this element in the RBA. Margie D. Lee, D.V.M., Ph.D., emphasized the risks associated with a food shortage or famine associated with a pandemic.

Dr. Koehler asked for a clarification of lines 329 and 330 of the draft framework, which read, "This also includes risks resulting from laboratory workers keeping intermediate hosts as pets." Dr. Berns explained that food animals, pets, and even wildlife should be considered in the RBA since they can serve as intermediate hosts that transmit a disease. Dr. Stanley noted that the sentence in question is far more specific than most of the other points. He suggested modifying that sentence to describe a more general risk to livestock and companion animals.

Dr. Berns said that economic risks presented an obvious yet complicated issue. The working group does not want the contractor to engage in time-consuming comprehensive economic analysis, but they did want to acknowledge the serious economic costs of any pandemic.

Dr. Miller said that the same approach could be used to include the risk of loss of public confidence in science. He suggested employing a similar approach in which the risks associated with loss of public confidence could be considered but not necessarily calculated.

Returning to the issue of biosafety, Dr. LeDuc said that Gryphon Scientific should be aware of the various BSLs and should perform analysis of the benefits and risks at each level.

Dr. Viggiani asked the NSABB whether they felt the draft framework captured all of the relevant risks. Dr. Resnick asked Dr. Viggiani whether there are additional risks that the government is interested in exploring. Dr. Resnick suggested expanding the focus of the RBA beyond agents with pandemic potential. Christine M. Grant, J.D., M.B.A., asked for clarification. Dr. Resnick

gave an example of modifying a bacterial organism to evade existing antibiotic approaches, which could result in significant localized events with high morbidity and mortality, but not a pandemic.

Dr. Berns said that type of risk is already addressed under DURC. Dr. Stanley said that these questions should be considered as the NSABB deliberates.

Benefits

Dr. Berns reintroduced the five benefit categories from the draft framework: scientific knowledge, biosurveillance, countermeasure development, informing policy decisions, and economic benefits. In particular, he asked the NSABB for input on the second benefit category, biosurveillance. He said that the recent outbreak of Ebola virus was a good example of the need for comprehensive public health surveillance, but surveillance of agricultural, domestic, and wild animals was equally important.

Dr. Stanley complimented the working group for developing a framework that incorporates many of the issues brought up in public discussions of GOF research.

Next, Dr. Berns invited comment on the categories of countermeasure development and informing policy decisions. Dr. Layton commented that some of the benefit categories specifically include language about the unique benefits provided by GOF research. She suggested that this language be added to every category or as a blanket statement applying to all the categories.

Scenarios and Events

Dr. Kanabrocki said that the goal of this section was to provide guidance to the contractor on which types of scenarios and events should be modeled in the RBA. He reviewed the 14 categories of events, and he asked for feedback on whether the list is missing anything or whether some of the events could be removed from the list.

Dr. Stanley asked whether the second and third categories, “Events that lead to direct infection of lab worker(s)” and “Accidental direct release into the environment, with possible public exposure,” were not just subsets of the first category, “Accidents due to equipment failure, human error, and system malfunction.” Dr. Kanabrocki agreed.

Dr. Stanley asked how the 13th category, “Accidents resulting from conduct of GOF research under substandard biosafety/biocontainment conditions or practices, either in the U.S. or internationally,” differs from the first, second, and third categories. Dr. Kanabrocki clarified that the 13th category is focused on the difference in risks between laboratory accidents in the right biocontainment settings and accidents in settings with inadequate biocontainment. Dr. Stanley asked how the RBA could quantify the eventual consequences of accidents in the two settings. Dr. Berns said that if the containment is substandard, then the downstream consequences will likely be magnified.

Dr. Berns asked for comment from Dennis M. Dixon, Ph.D., of the Bacteriology and Mycology Branch at the National Institute of Allergy and Infectious Diseases. Dr. Berns asked whether there are ongoing conversations at the international level about policies surrounding GOF studies. Dr. Dixon responded that extensive discussion has taken place domestically since the

government announcement in October. Subjects have included assessing increasing pathogenicity and what entails a reasonable likelihood of increasing pathogenicity and transmissibility; however, he was not aware to what degree these issues are being discussed internationally. They have reviewed published experiments that may have involved GOF research, but which may have been performed before the U.S. government began its deliberations.

Christopher T. Park, Director of the Bureau of International Security and Nonproliferation, noted that international discussion is ongoing, but the degree of concern about GOF research varies by country. Mr. Park said the issue has arisen at meetings of the Biological and Toxin Weapons Convention and the Global Health Security Initiative. Within individual countries, most discussion of GOF research is combined with discussion of dual-use research. The German Ethics Council has called for extensive regulation, and Dutch policy makers are reviewing their policies and practices. A French committee similar to the NSABB has been proposed. Dr. Park said that work on the subject may be underway in Asia, but he does not know the details. He concluded by emphasizing that the United States is at the forefront of this conversation and will lead by example.

Dr. Dixon asked how many of the international examples were specific to GOF research. Mr. Park said that none of them were explicitly focused on GOF studies but that the discussions have often focused on the same journal articles that sparked the U.S. moratorium. Dr. Stanley noted that current international conversations about GOF research will be relevant as the NSABB addresses Deliverable 2.

Dr. Morse asked Dr. Kanabrocki to elaborate on event category 14, "scenarios based on alternative experimental approaches to GOF research." Dr. Kanabrocki said the intention was to model different approaches that might ultimately achieve the same outcome as GOF research and to weigh the relative risks of those approaches. Dr. Berns added that one avenue may be computational approaches.

Biosafety Assumptions

Dr. Kanabrocki said that for each agent analyzed in the RBA, multiple BSLs will be assessed and the effects of each level on event scenarios will be determined. This analysis will provide insight into how higher containment levels or more robust safety programs may mitigate some of the risks presented by GOF research.

Dr. LeDuc suggested taking a more granular approach to biosafety, moving beyond biosafety levels to look at individual techniques and practices. Dr. Kanabrocki said that that approach might be better used in Deliverable 2. For the RBA, the working group recommended examining not only BSL1, BSL2, BSL3, and BSL4, but also permutations like agricultural BSLs and enhanced BSL3.

Dr. Viggiani asked whether the committee agreed that the RBA should include a range of biosafety containment, and practices, or whether NSABB members believed it would be more advantageous to focus only on the BSL required according to current guidances for the experiment being modeled. Dr. Kanabrocki said he preferred modeling a range, which can provide a more realistic simulation of the international research landscape. Marie-Louise

Hammarskjöld, M.D., Ph.D., agreed. She added that the RBA should also consider the practices used within each BSL.

Dr. Berns concurred, again citing the recent Ebola virus situation, in which changing burial practices helped stop the epidemic's spread. Dr. Resnick agreed. Ms. Wolf agreed as well, adding that there are situations in which the BSL is unknown or inadequate.

Dr. Stanley invited comment from *ex officio* and *ad hoc* members of the Board.

Diane DiEuliis, Ph.D., deputy director for policy in the Office of the Assistant Secretary for Preparedness and Response at the Department of Health and Human Services, said that within her organization, they focus on the most likely negative outcomes. She noted that the working group's draft framework included categories of risk and that each proposed risk scenario should fit into one of these categories. Dr. DiEuliis observed that biosafety is listed as a category of risk but not risk mitigation. She said that similar mitigations will exist for each category.

Edward H. You, a special agent with the Biological Countermeasures Unit of the Weapons of Mass Destruction Directorate of the Federal Bureau of Investigation, suggested an alternative approach to selecting agents to include in the RBA: considering outcomes of concern. He said that looking at both positive and negative outcomes may help categorize which elements to include. He offered the recent example of gene drive experiments that established traits in *Drosophila* within one generation. He said that similar tools could be used to produce immunocompromised hosts, which could lead to pandemics without modifying a pathogen. To that end, the NSABB should consider consulting security agencies to learn more about outcomes of concern. He also suggested investigating which organizations perform risk assessments in these areas.

Gerald Epstein, Ph.D., deputy assistant secretary for chemical, biological, radiological, and nuclear policy at the Department of Homeland Security, directed the Board's attention back to the framework draft. He pointed out lines 220–222, which read, "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." Dr. Epstein said that many of the risks and benefits listed are not outcomes of specific research but instead are the results of sequences of events, which may be more or less likely in the presence of GOF research. He said that risks and benefits are not automatic and that other factors are involved.

Mr. Park urged the NSABB to consider a narrow focus for the RBA. He said that the assessment will not be the conclusion of the process, rather a critical component of deliberations and the policy formulation process. Every element of the RBA will be scrutinized, thus should be unassailable. The more pathogens and scenarios involved, the more complicated the assessment will be, and errors may be more likely to appear. Mr. Park expressed a preference for an assessment that is focused and accurate, one that leads to a policy outcome. Such an assessment may not be as broad as originally desired, but it will allow policymakers to address the issue. In the future, the model could be replicated or expanded.

Public Comment I
Dr. Stanley invited those interested in making comments to do so.

Gregory Frank, Ph.D., a program officer for science and research policy at the Infectious Diseases Society of America (IDSA), said that IDSA physicians are among the first responders to care for infected individuals during any microbial disease outbreak. Therefore, they are well positioned to understand the risks and benefits posed by GOF research and can provide valuable input. Dr. Frank commended the draft framework but noted that the IDSA believes it can be improved. To fully understand the risks of GOF research, it is critical to include the following factors:

- The pathogen being investigated
- The number of investigating laboratories and personnel performing the research
- The BSLs of those facilities
- The period of time for which the research will be conducted

Dr. Frank said that the IDSA also recommends that the NSABB place more emphasis on the timeline of potential benefits when particularly risky research has been proposed. He said that the IDSA is concerned that the framework may create barriers to the rapid development and production of vaccines, especially for influenza.

Dr. Frank said that the IDSA is committed to ensuring the participation of the scientific and science policy communities in these deliberations. To complement the NSABB's efforts, the IDSA calls for a continued series of discussions on the subject with all stakeholders. The IDSA will submit additional written comment to the NSABB after the meeting.

Nicholas Evans, Ph.D., a researcher in the Department of Medical Ethics and Health Policy at the University of Pennsylvania, commented on a number of issues in the draft framework. Citing concerns about transparency and conflicts of interest, he said that the document does not explicitly list the working group members, advisors, or *ex officio* government representatives involved. Dr. Evans said that no explanation was given for the selection and contracting of Gryphon Scientific. He questioned how this selection was made prior to the completion of the framework.

On the subject of deliberative neutrality, Dr. Evans noted that no basis was provided for the composition of the working group. He said that the framework described the RBA as a collaborative process between the NIH, the NSABB, the National Academies of Science, and Gryphon Scientific, but the details and limits of this collaboration are not communicated.

Dr. Evans said the framework draft made use of the concept of reasonableness without providing a definition. He said that meanings of this term vary widely; therefore, the NSABB's recommendations regarding reasonableness were unclear. He noted that in the draft framework, the pursuit of therapeutics is listed as a potential benefit, but surveillance is not. He cited a National Research Council analysis demonstrating the need for GOF alternatives for purposes other than therapeutic development. He said that the overall benefits and risks in the framework were not well defined.

Dr. Evans shared a list of issues his colleagues had mentioned: not including information security as a biosecurity concern, overlapping risk categories, not including biodefense as a biosecurity risk, making no distinction between biosecurity and dual-use research, and not including circulation of dual-use information in the list of risk scenarios.

Thomas V. Inglesby, M.D., CEO and director of the Center for Health Security at the University of Pittsburgh Medical Center, said that he and Marc Lipsitch had made specific recommendations for the RBA in earlier publications. He asked what Gryphon Scientific's strategy would be for evaluating claims of benefits. Dr. Inglesby said it was important to recognize that some human error is inevitable in any setting, even the most secure. He observed that the framework makes relatively little mention about how to evaluate insider threats. He said that information risk is important to this assessment but will be hard to assess. Dr. Inglesby said that the deliberative process to date has not engaged the public health or clinical community in a meaningful way, even though the immediate consequences of a laboratory accident or deliberate misuse would affect those communities first. Also there has been very little international engagement and no real public engagement. He said that inviting members of the public to speak at a single meeting for three minutes was not reasonable, and he expressed a hope that there will be more opportunities for serious engagement with the public. Dr. Inglesby concluded by saying that the NSABB needs to begin to determine whether there are any lines that should not be crossed in GOF research.

In response to Dr. Inglesby's comments about outreach, Dr. LeDuc asked the NSABB whether a plan has been articulated for greater public engagement. Dr. Wolinetz said that another forum has been planned at the National Academies of Science. She noted that even after Deliverable 2 is complete, the public will still have opportunities to participate in the deliberations as the government considers new policies on GOF research. Dr. Viggiani added that the NSABB was selected for this task in part because it is a federal advisory committee, meeting publically, with opportunities for public comment. He invited suggestions on additional methods of collecting public input.

NSABB Discussion on Draft Framework; Vote to Approve If Appropriate
Samuel L. Stanley, Jr., M.D.

Dr. Stanley thanked the commenters for their contributions. He asked Dr. Viggiani to summarize the suggested amendments to the draft framework.

Dr. Viggiani listed the following changes:

- Add a fifth pathogen characteristic: the evasion of medical countermeasures or increase in drug resistance.
- Edit the pathogen characteristics section to use more general language and describe pathogens, not viruses.
- In the category of agricultural risk, change the word "pets" to "companion animals" or "intermediate hosts."
- Add a risk category for the loss of public confidence. This category will be considered generally and not calculated quantitatively.

- Add a sentence to the benefit categories section to make it clear that all benefits listed should be unique to GOF studies.
- Begin with existing biosafety guidance when modeling new scenarios and include a range of biosafety and containment scenarios in the RBA.

Dr. Viggiani said that NIH staff will incorporate these edits. No additional substantive edits will be made without consulting the NSABB.

Dr. Stanley invited the Board to vote on approval of the draft framework. The motion carried unanimously and the framework document was approved.

Lunch
The meeting adjourned for lunch at 11:45 a.m. and resumed at 12:46 p.m.

Methods and Approaches to Conducting Risk and Benefit Assessments of Gain-of-Function Research
Rocco Casagrande, Ph.D.,Managing Director, Gryphon Scientific

Dr. Casagrande outlined Gryphon Scientific's overall approach to the RBA. He said his team has divided the RBA into three major tasks, each of which requires a distinct data collection and analysis approach:

- Biosafety risk analysis, which will involve quantitative modeling of the probability and consequences of various events that could lead to an outbreak
- Biosecurity risk analysis, which will involve analysis of data from intelligence and law enforcement communities, as well as an assessment of security measures
- Benefit assessment, which will involve understanding the gaps in scientific knowledge, public health, and medicine that GOF experiments could uniquely address, as well as recognizing the scientific and non-scientific barriers to the realization of these benefits.

Dr. Casagrande said that considering timeframes is very important in order to ground the RBA in evidence. He said that the assessment will use a five-year horizon for all risks. For benefits, foundational science must occur within a five-year timeframe, but it is understood that the benefits will follow in time.

Dr. Casagrande introduced the Gryphon Scientific team members who will be leading the assessment:

- Mark Kazmierczak, Ph.D., biosafety risk analysis
- Bob Stephan, retired colonel, U.S. Air Force, and Kavita Berger, Ph.D., biosecurity risk analysis
- Carissa Meyer, Ph.D., benefit assessment

Dr. Casagrande explained that Gryphon Scientific is the prime contractor, supported by the subcontractors, Signature Science and Abt Associates. He reviewed Gryphon Scientific's recent work performing RBAs for the planned National Bio and Agro-Defense Facility, for federal guidance to the industry that makes custom synthetic nucleic acids, for evaluating the contents of

the Strategic National Stockpile, and to evaluate triage priorities after a nuclear attack. He said that Gryphon Scientific hopes to provide similar guidance to the NSABB so that, when developing policy recommendations, all stakeholders will have a consistent foundation of evidence.

Dr. Lee commented that food security issues seemed to be absent from the RBA overview. Dr. Casagrande said that the analysis is primarily focused on human morbidity and mortality. Secondary issues like transportation or utility disruptions and food security are not part of the initial assessment, but they may be investigated later if the initial assessment is favorably received.

Ms. Wolf asked Dr. Casagrande to clarify the intended geographic range of the assessment. Dr. Casagrande said the RBA will examine biosafety and biosecurity risks in a global context and consider the potential globalization of benefits.

Biosafety Risk Assessment Methodology

The biosafety risk assessment will have several elements. Frequency—of experiments, accidents, and natural disasters—is a major component. Gryphon Scientific will examine numerous potential pathways to an infection occurring outside of the laboratory. Dr. Casagrande and his team will estimate the probability that outbreaks occur due to accidents and natural disasters and estimate the consequences of a resulting outbreak in the human population surrounding the laboratory and internationally. They will consider models of human and animal outbreaks, local outbreaks, and international pandemics.

To best support decision-making, Gryphon Scientific will provide information to help the NSABB answer a range of hypothetical questions, including:

- How would risk change if the number of sites performing this work were to increase?
- How would risk change if the work were performed with different containment measures?
- How would the risk change if transmissibility, pathogenicity, or countermeasure resistance were increased?

The answers to these questions can help clarify the conditions under which this work could proceed safely, if such conditions exist. Dr. Casagrande said it is possible that the RBA will conclude that some locations, experiments, and sites are too risky to justify the potential benefits of GOF research, while others might pose an acceptable risk.

Dr. Casagrande said one of the challenges of this project is to assess the risk of experiments that have not yet been performed in places that have not previously performed such work. To answer this question, Gryphon Scientific has taken a parametric approach, exploring how changes in key features of the pathogens, containment measures, and laboratory conditions affect risk.

Gryphon Scientific will use specific pathogens as examples. Phenotypic description of pathogens will focus the RBA on the characteristics of pathogens that will drive risk. The three pathogens selected for inclusion by the NSABB will be characterized as exemplars to anchor the parametric analysis in real-world science. This method enables the comparison of risk from GOF research of

concern to that already accepted for research on unmodified pathogens. Parametric description of containment practices can also help semantic arguments over what constitutes various BSLs.

Dr. Casagrande's team will use sensitivity analysis to identify drivers of risk and how elements of containment, and pathogens can affect risk. He demonstrated a tornado plot, which helps define the extent to which a given parameter or variable can affect risk. Some parameters may prove to have little effect on overall risk. For those that have a significant effect on risk, it is important to understand how they drive risk.

Biosecurity Risk Assessment Methodology

The biosecurity risk assessment will have two main components: a semi-quantitative assessment of the risks of intentional acts against the laboratory, causing infections outside the laboratory, and an assessment of the potential for misuse of the information generated by GOF research.

Gryphon Scientific will identify the types of actions that hostile actors could attempt against GOF laboratories and estimate their probability of success given known capabilities of the offense and defense. Dr. Casagrande's team has divided hostile actors into several categories and listed potential behaviors of concern. They hope that by understanding the capabilities of these adversaries and the capabilities of the defense, they can calculate risk per attempt. Questions they will ask include, "How likely are these people to be successful?" and "What are the likely consequences of a successful hostile act?" Understanding the frequency and risks associated with these acts will allow the NSABB to determine which biosecurity threats are great enough to render GOF research too risky to perform. This semi-quantitative method focuses on concrete, accessible, and reliable data from the law enforcement and intelligence communities. Some of this data will be classified, but the analysis will be presented in an unclassified manner and available to the NSABB and others making policy recommendations and decisions.

The risk of misuse of the information generated by GOF research will be comparative. Gryphon Scientific will attempt to answer the following questions:

- What can various actors accomplish with the biological agents that already exist or are already described in the literature? What do the new phenotypes afford a hostile actor compared to what these agents can already do?
- What additional capabilities are afforded by GOF research compared to other ongoing research topics and existing studies?

Intelligence and law enforcement data will be used to determine whether these unique capabilities are desired by various groups and whether the publishing of additional pathways to dangerous pathogens drives the risk of misuse. The assessment will determine whether information risks increase with frequency of publishing GOF experimental results. If Gryphon Scientific finds that the unique capabilities afforded to pathogens by GOF studies exist and are desirable to hostile actors, team members will use data from law enforcement to characterize the resources and skill needed to replicate these qualities. Dr. Casagrande noted the importance of incorporating the knowledge investment required for many hostile acts against laboratories.

Dr. Resnick asked whether the analysis examined relationships between threat and vulnerability. He noted that an earthquake does not choose which laboratory to strike, but aggressors may

select attack sites specifically for their vulnerabilities. Dr. Casagrande said there are two questions to consider:

- To what extent are hostile actors aware of where GOF research takes place?
- What is the ability of these actors to scout for vulnerable locations?

Both questions investigate not only the capabilities of hostile actors but also their knowledge and intent.

Qualitative Benefit Assessment

The benefit assessment will use a systematic approach to identify opportunities, barriers, and competing pathways to benefits. Gryphon Scientific will use a variety of data sources:

- Stated benefits from researchers proposing to do this work and those who have performed similar work
- Stakeholders in the consumer, commercial, and scientific sectors, as well as critics of GOF studies
- Governmental and semi-governmental body guidance

The assessment will also consider the parallel opportunities afforded by alternative modes of research.

Dr. Casagrande said that understanding the barriers to potential benefits is an important element. The assessment will attempt to understand the gaps in scientific knowledge that can be addressed by this type of research and how likely these benefits are to be realized.

Gryphon Scientific has characterized the benefits of GOF and alternative research by four parameters: research opportunities, potential benefits, barriers to those benefits, and whether those benefits exist. To consider the globalization of benefits, Gryphon Scientific is performing a qualitative analysis to examine how public health benefits in the last several decades have globalized.

Questions from the NSABB and Discussion

Dr. Layton asked for clarification as to how Gryphon Scientific will incorporate the three viruses selected for the RBA. Dr. Casagrande explained that the parametric analysis should enable analysis not only of the particular pathogens but also encompass pathogens and pathogen classes with similar traits. He said that the example pathogens will be used as landmarks to ground the analysis in concrete data.

Dr. Layton asked Dr. Casagrande to elaborate on the collection of qualitative data for the benefit analysis. Dr. Casagrande said that many of the potential benefits will be highlighted in public health literature. The analysis will cross-reference these benefits with those identified in non-biomedical literature. Gryphon Scientific will interview investigators, public health and biosecurity experts, members of the commercial sector, and government stakeholders. Dr. Layton asked whether these interviews would address benefits unique to GOF research, and Dr. Casagrande confirmed that they will.

Ms. Wolf requested further clarification on the planned parametric analysis of pathogens. Dr. Casagrande said that describing viruses parametrically captures a great deal of theoretical space

and will yield information that describes not only pathogens that are currently of concern but also those that may arise in the future. He acknowledged that there are some shortcomings in the method, as it does not incorporate, for example, vector-borne illnesses, but the assessment should comprehensively analyze the risks for the listed pathogens of concern and those like them.

Ms. Wolf noted that the NSABB had discussed adding a bacterial pathogen to the RBA. She asked Dr. Casagrande whether he felt the framework would still be helpful without it. Dr. Casagrande said that it depends on the pathogen. He said that bacterial pathogens, as long as they were similar in transmissibility and pathogenicity to the viruses included, should be well modeled in the current framework.

Ms. Grant said that the working group felt it was important to describe the nature of the evidence being used. She asked how the RBA will account for different qualities of evidence. Dr. Casagrande said that Gryphon Scientific is known for understanding the evidence basis of conclusions and presenting that basis in a transparent fashion. He said that the assessment will highlight, rather than mask, any uncertainty in the data so that decision-makers will recognize when conclusions are evidence based and when they are not. Dr. Casagrande said that uncertainty can be modeled like any other parameter and will be included in the assessment.

Ms. Grant asked how Gryphon Scientific will evaluate different types of risk against benefits of a different nature. Dr. Casagrande said that the RBA intends to make relative statements. Dr. Casagrande acknowledged that it is not constructive to compare different types of risk or benefits as though they were the same; all the assessment can do is evaluate increases in risks and benefits. The RBA will note whether or not a risk will change significantly and whether benefits are significant and the types of barriers to their realization.

Dr. LeDuc noted that the plan for the benefit assessment includes parallel analysis of alternative research methods. He asked whether the same would be true for the biosafety risk assessment. Dr. Casagrande agreed that it should be. Dr. LeDuc said that the risks of certain events, like natural disasters, will be the same regardless of the type of experiment. Dr. Casagrande agreed, but he noted that the consequences will be different. He added that there are more labs performing alternative studies than GOF research, which will also affect the assessment.

Referring to the graphs plotting individual pathogens on a field of pathogen characteristics, Dr. Morse asked how the quadrant lines of those graphs will be located in the RBA. Dr. Casagrande said that the placement will be driven by the nature of the data. In many of the other epidemiology analyses Gryphon Scientific has performed, clear breaks in the data have emerged, but there is no way of predicting whether that will be the case for this assessment. Dr. Casagrande added that transmissibility will be divided into humans, other mammals, waterfowl, and other birds to achieve the most granular and data-driven results.

Dr. Morse asked how qualities and characteristics can be parameterized in a way that allows comparison. Dr. Casagrande said risks can be denominated quantitatively, as in number of human deaths per year, or by using the Monte Carlo method to assign a risk level for each element.

Dr. Morse asked how alternatives to GOF research will be identified. Dr. Casagrande said the assessment will compare research that is subject to the moratorium with research that is not.

Dr. Lee observed that there is a sizeable gap between the risk and benefit categories presented by Dr. Casagrande and those outlined in the framework document. She asked how those discrepancies would be resolved. Dr. Viggiani said that over the next month, Gryphon Scientific will create a work plan, which will be shared with the NSABB working group. At that time, the working group will determine whether the work plan is satisfactory and whether the full NSABB needs to assemble to discuss the work plan before approving it.

Dr. Stanley added that the process will be dynamic and iterative. He said that while Gryphon Scientific's work plan should align with the NSABB's framework, the Board must be realistic and recognize that it may not be possible to model every recommended element in the allotted timeframe.

Dr. Resnick said that the RBA must produce risks and benefits that can be compared. Dr. Stanley said that the assessment can only work with the available data and that it will be difficult to find concrete numbers on potential benefits. For this reason, the RBA will be only one element informing the Board's deliberations.

Discussion of Upcoming NSABB Deliberations: Identifying Information and Expertise to Develop Recommendations

Susan Wolf, J.D., Member, NSABB
McKnight Presidential Professor of Law, Medicine, and Public Policy, Faegre Baker Daniels Professor of Law, Professor of Medicine, Faculty Member, Center for Bioethics, University of Minnesota

Joseph E. McDade, Ph.D., Member, NSABB
Deputy Director (Retired), National Center for Infectious Diseases, Centers for Disease Control and Prevention

Dr. Stanley congratulated the working group on their work to date and asked Drs. Berns and Kanabrocki to remain in their roles as co-chairs. He invited other members of the NSABB to consider joining the working group as well.

Dr. Stanley said that the NSABB has two remaining tasks. The working group will continue to weigh on the conduct of the RBA, and the entire NSABB will develop draft recommendations for evaluating proposed GOF studies. He invited Ms. Wolf and Dr. McDade to present the next steps for these tasks.

Ms. Wolf noted that she was speaking on behalf of herself and Dr. McDade, who was unable to attend the meeting in person but was participating via teleconference.

Ms. Wolf reiterated that developing Deliverable 2 will require more than the results from the RBA. She said that the data may be suggestive, but that numerical and even qualitative information cannot provide the ultimate answers. The NSABB will need to interpret the information the RBA will generate. She offered the following questions for consideration:

- What does the risk-benefit analysis tell us about the relative risks and benefits associated with the GOF studies involving pathogens with pandemic potential?
- Are there particular GOF studies that raise significant concerns?
- What are the ethical and policy considerations that should guide decisions about GOF studies?
- Do current policies, regulations, and guidelines adequately address and mitigate the potential risks of GOF studies involving pathogens with pandemic potential? Is additional oversight needed?
- How does GOF research fit into the overall scientific research and public health endeavor and the NIH portfolio?

Ms. Wolf introduced the timeline for the remainder of the deliberative process. She said that the next phase is policy analysis, research, and information gathering, including examination of the U.S. government and international policies, briefings from subject matter experts, and readings. By August 2015, the next phase will begin by interpreting and synthesizing the information gathered. In the final phase during early 2016, the NSABB will draft its recommendations. The draft should be ready before the second National Academies of Science forum so that they can be presented for discussion.

Ms. Wolf presented a list of topics the working group would like to address during the second phase and the types of input they would like to collect. These include:

- Domestic policy: Review of U.S. government policies relevant to DURC, GOF research, and oversight of research involving pathogens
- International policy: International regulations and policies on biomedical research related to DURC and GOF research; relevant U.S. commitments under international law; summaries from relevant international meetings; proposed new policies on DURC or GOF research; and materials issued by international scientific and public health societies, advocacy organizations, and other organizations.
- Funding agency perspectives: Presentations from U.S. government agencies and non-governmental funding bodies, including descriptions of project review processes and discussion of how GOF studies fit within a broader research portfolio
- Broad scientific perspectives: Perspectives on GOF research from highly respected scientists from diverse fields, including non-GOF research, in general microbiology, synthetic biology, neuroscience, or other fields, as well as clinicians and public health experts
- Ethics and policy choices: A commissioned review of ethical writings and frameworks for generating policy recommendations informed by risk-benefit analysis, and briefings from those with expertise in creating DURC policy
- National security: National security briefing to the NSABB and biosecurity analysis as part of commissioned risk assessment
- Science communications: Perspectives from journal editors and publishers and science reporters about how GOF studies fit within a broader scientific context, how they are reviewed by journals, why they are published, and what they contribute to the knowledge base, as well as how they are received by the scientific community and public
- Sample limiting case: A review of the literature describing the history of the smallpox eradication and the decision-making process for restricting smallpox research

Ms. Wolf invited questions and comments from the NSABB.

Dr. Layton suggested that the vaccine and therapeutics industry should be included in the "broader scientific perspectives" category. She asked whether the question of public engagement had arisen in working group meetings. Ms. Wolf said that it had, and asked Dr. Layton whether she had any recommendations. Dr. Layton acknowledged that it may be challenging to engage the public thoroughly on this timeline. She offered the example of the discussions in the early 2000s about smallpox vaccination. She said the outreach was rigorous and included well-attended public forums in a number of U.S. cities.

Dr. Stanley invited comment from *ex officio* and *ad hoc* members of the Board.

Mr. You said that the proposed RBA seems very robust. He asked who will take responsibility for managing the review of proposed GOF studies, and recommended including Institutional Biosafety Committee (IBC) members in the review panels, as they may already have assessment processes in place. Ms. Wolf said the eventual review recommendations cannot yet be predicted but that including IBC is a good suggestion.

Camille Harris, D.V.M., Ph.D., M.S., wildlife disease coordinator for the U.S. Geological Survey, said she noticed that wildlife was mentioned in the draft framework and in the presentation by Dr. Casagrande. She recommended that the NSABB be mindful of the fact that changes in transmissibility or pathogenicity may affect persistence of an agent in the environment, as well as how the agent may react in different animals. She encouraged Gryphon Scientific to call upon the U.S. Geological Survey for data on H5N1. Dr. Casagrande agreed that it important to examine human risk as it relates to wildlife and domestic animals and said these elements will be included in the assessment.

Public Comment II
Dr. Stanley invited those interested in making comments to do so.

Lone Simonsen, Ph.D., a professor of global health at George Washington University, said she has studied pandemic influenza and other emerging infectious diseases for the last 20 years and has thought a great deal about GOF research. She commended the draft framework and said that as a mother, she feels she has a responsibility to her children to be part of a group that makes the right decisions about GOF research. She said she thought the RBA should include emerging threats, but she recognized that specific pathogens of concern will change over time.

Peter Hale, executive director of the Foundation for Vaccine Research, said that there are some lines in research that should probably never be crossed. He cited a recent public statement by NIH Director Francis Collins in which he announced that NIH will not fund studies of gene editing in human embryos.

Dr. Hale presented data from a recent *ad hoc* meeting on GOF research. The meeting produced three primary conclusions:

- GOF research, especially experiments to increase the transmissibility of highly pathogenic avian influenza viruses, is a precedent-setting case study for the regulation and oversight of research.
- Because this is a high-stakes issue that could affect the entire world, there is a need for genuine public engagement, including civil society. This research is conducted with taxpayer money, and the taxpayers should be consulted.
- There may be some types of experiments that can be taken off the table right now. Meeting attendees proposed a process, distinct from the NSABB deliberations, to help policy makers identify and define which types of research should not be performed and which types can be performed under specific circumstances.

Dr. Hale shared charts to support his statements. He agreed to send those charts to the NSABB via email.

Andy Kilianski, Ph.D., a National Research Council fellow with the U.S. Army, shared his comment as a private citizen. He said that the United States is an excellent place to perform life sciences research. Dr. Kilianski noted that the framework did not mention the risks of funding or not funding GOF research and how those decisions will affect the intellectual capital maintained in the United States, and therefore national defense. He said it would behoove the community and the Board to consider these issues further as the deliberations proceed.

Kanta Subbarao, M.B.B.S., M.P.H., a senior investigator at the National Institute of Allergy and Infectious Diseases, asked the Board to consider assessing the risks of not conducting certain types of research. She cited the examples of antigenic drift in seasonal influenza viruses and research to develop universal influenza vaccines.

Closing Remarks and Adjournment

In closing, Dr. Stanley commended the day's discussions. He thanked the members of their working group for their hard work in preparing the draft framework, and he urged other members of the NSABB to consider bringing their expertise to the working group. He thanked Ms. Wolf and Dr. McDade for laying out a path for the next steps, and all the Board members, public commenters, and *ex officio* members for their willingness and input. He adjourned the meeting at 2:54 p.m.