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NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY (NSABB)

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NIH Campus
9000 Rockville Pike
Building 31, Floor 6C, Room 6
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.
J. Patrick Fitch, 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., CBSP
Theresa M. Koehler, Ph.D.
Jan Leach, Ph.D.
Marcelle C. Layton, M.D.
James W. LeDuc, Ph.D.
Francis L. Macrina, Ph.D.
Joseph E. McDade, Ph.D.
Stephen S. Morse, Ph.D.
Jean L. Patterson, Ph.D.
I. Gary Resnick, Ph.D.
Susan M. Wolf, J.D.
David L. Woodland, Ph.D.

ABSENT
Margie D. Lee, D.V.M., Ph.D.
Jeffrey F. Miller, Ph.D.
Rebecca T. Parkin, Ph.D.

EX OFFICIO MEMBERS/FEDERAL AGENCY REPRESENTATIVES
Susan Coller-Monarez, Executive Office of the President
Diane DiEuliis, Ph.D., Department of Health and Human Services
Dennis M. Dixon, Ph.D., National Institutes of Health
Gerald Epstein, Ph.D., Department of Homeland Security

M. Camille Harris, D.V.M., Ph.D., M.S., Geological Survey
Betty Lee, Ph.D., Department of Commerce
David R. Liskowsky, Ph.D., National Aeronautics and Space Administration
Christopher J. Park, M.S., Department of State
Michael W. Shaw, Ph.D., Centers for Disease Control and Prevention
Eileen Thacker, Ph.D., D.V.M. Department of Agriculture
Christopher J. Viggiani, Ph.D. National Institutes of Health, Executive Director, NSABB
Sharlene Weatherwax, Ph.D., Department of Energy
Carrie D. Wolinetz, Ph.D., National Institutes of Health

WELCOME AND INTRODUCTIONS

Opening Remarks

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

Dr. Stanley opened the meeting at 8:30 a.m. with a welcome to all in attendance, including those who were watching online.

He reviewed the NSABB's work so far. In October 2014, the government paused funding of certain gain-of-function (GOF) studies and launched a deliberative process to re-assess the risks and benefits associated with them. The NSABB and the National Academies of Sciences, Engineering, and Medicine are part of the reevaluation process.

Although GOF studies can provide valuable information about host–pathogen interactions that could help protect against a pandemic, involving influenza, SARS, and MERS, they can also pose biosafety and biosecurity risks. A GOF study could enhance a biological agent's pathogenicity or transmissibility and the risk exists that an enhanced pathogen could be accidentally or intentionally released from a laboratory. GOF studies can also generate research information or products that could be misused by those with malevolent intent.

The NSABB was issued a two-part charge as part of the deliberative process. The first was to advise the design and conduct of a risk–benefit assessment (RBA) of GOF studies. The RBA will help inform the Board's second charge – the development of recommendations to the USG on how to evaluate proposed GOF studies. The National Academies held the first of two meetings on the GOF issue in December 2014, which included robust discussion by domestic and international stakeholders that have informed the NSABB's deliberations to date. A second NAS meeting will be held March 2016. In May the NSABB accomplished its first task when it finalized a framework for guiding the RBA. Towards its second task, the NSABB also formed a working group to further examine a number of issues identified by the Board in its discussions.

Dr. Stanley stated that the meeting would include a progress report by the NSABB Working Group on Evaluating Risks and Benefits of GOF Studies, a presentation from Gryphon Scientific regarding its progress on the RBA, and a panel discussion on ethical, legal, and and policy issues associated with GOF studies. He also mentioned that, as part of the discussions, bioethicist Dr.

Michael Selgelid would present his ongoing analysis of ethical issues related to GOF research, which was commissioned by the USG to inform the NSABB on this important area of consideration.

Dr. Stanley encouraged public input on the issues associated with GOF studies from all interested parties both during the meeting and via email to the Board at nsabb@od.nih.gov.

Dr. Stanley also noted that the government policy for institutional oversight of life sciences dual use research of concern (DURC) became effective in September 2015. The new policy requires that funding agencies and institutions identify DURC in their portfolios and develop mitigation plans when necessary. The NSABB played a role in the development of the policy and looks forward to following its implementation.

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

Dr. Viggiani invited board members and *ex officio* members—those present and those attending via teleconference—to introduce themselves.

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

Dr. Viggiani explained that the NSABB is an advisory committee that operates in accordance with the Federal Advisory Committee Act and that NSABB members are considered Special Government Employees and 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 minutes of the May 2015 meeting were reviewed and unanimously approved.

UPDATE FROM THE NSABB WORKING GOUP

Update from the Working Group on Evaluating Risks and Benefits of GOF Studies Involving Pathogens with Pandemic Potential
Joseph Kanabrocki, Ph.D., CBSP, Co-chair, NSABB Working Group
Associate Vice President for Research Safety, Professor of Microbiology, University of Chicago

Dr. Kanabrocki began by emphasizing that his presentation of the working group's preliminary findings should be considered a draft as the working group was still in the process of gathering and analyzing information.

He stated that GOF refers to any modification of a biological agent that confers novel or enhanced .properties and GOF studies are thus not a new phenomenon. However, a subset of these studies, those that could enhance pathogenicity or transmissibility of certain pathogens, has caused concern. Although these studies are conducted for legitimate reasons, there is debate about whether the risks and benefits are properly balanced.

The NSABB has already completed one of its two tasks: the framework for the design and conduct of the RBA, which the board approved in May. The framework is available on the NSABB website and was developed to guide NIH as it manages Gryphon Scientific in conducting the RBA. The framework outlines the principles to guide the RBA, describes the risks and benefits to analyze, and recommends the types of pathogens, pathogen characteristics, and GOF studies to be examined.

The current NSABB working group was formed to provide input on the RBA and to develop draft recommendations on a conceptual approach to the evaluation of proposed GOF studies. The working group is composed of NSABB members and representatives of federal agencies with experience across a variety of disciplines.

Gryphon Scientific reviewed their work plan with the working group and the group agreed that Gryphon's plan, in general, was in line with the recommendations set forth in the NSABB's framework.

The Gryphon study will focus on human health and safety. Working group members noted that it will be difficult to compare benefits and risks, because the benefits will be qualitative, while risks will be quantitative. This may be unavoidable, but the working group asked Gryphon to express their findings in ways that facilitate comparisons.

Some working group members wanted to be sure that the benefits and risk analysis would include not only the identification of unique GOF benefits and risks , but also an examination of the benefits/risks associated with alternatives to GOF studies or of not doing GOF studies at all.

The working group's main task was to begin developing recommendations on a conceptual approach for guiding funding decisions for GOF studies. They approached this task in three phases: 1) information gathering; 2) interpretation, analysis, and synthesis; and 3) development of recommendations. Dr. Kanabrocki noted that the working group has begun phase two. The group expects to have draft recommendations ready in January and final recommendations in the spring.

Dr. Kanabrocki went on to describe the working group's deliberations to date, which began in May with an in-person meeting and several subsequent teleconferences. The group examined existing domestic and international policies, examples of GOF research, and various stakeholder perspectives.

Dr. Kanabrocki noted that oversight can occur at three different stages of research—funding, research conduct, and communication—but that emerging technologies are challenging the traditional oversight frameworks.

Biosafety oversight for pathogen research begins at the funding stage and continues throughout the course of the research. U.S. policies for oversight include general biosafety policies and guidance, select agent regulations, two policies on the oversight of dual use research, the HHS framework for guiding funding decisions about certain GOF studies, and export control regulations. Different policies are defined by different scope and applicability requirements and therefore, may or may not apply to GOF studies, depending on the pathogen, funding source, and experimental manipulation. Not all research involving pathogens poses the same level of risk. The board's challenge will be to determine whether there are GOF studies that are not adequately policed by current policies.

Biosafety, biosecurity, dual use, and GOF issues are being discussed globally and international funders are increasingly aware of both dual use research of concern (DURC) and GOF research. Current biosafety oversight for pathogen research in other countries is similar to the approach taken by the United States, in which biocontainment and laboratory practices are based on an assessment of risk. For example, Germany and Canada require that certain GOF studies with highly pathogenic avian influenza be performed using biosafety level 4 (BSL4). There are also differences; for example, some countries do not regulate pathogen research through funding agencies.

The working group considered different potential policy approaches to manage risk:

- A permissive approach that would allow the activity to proceed unless risks were clearly present.
- A precautionary approach that would limit activities unless protections were clearly present.
- An adaptive approach that would take a systematic approach to control risk in the face of uncertainty.

The working group noted that it is a challenge to manage risks associated with emerging technologies and new drugs, particularly as more people have access to life sciences research and as more options for funding become available, including crowdsourcing.

The working group spoke with science journal editors who said that they review manuscripts for biosecurity concerns. However, the editors generally felt that it is difficult to manage the risks of DURC at the publication stage and opposed redaction because of concerns about reproducibility. Some suggested that the government establish a committee to help them assess risk. The editors also said that the trend toward open access would make it difficult to manage risk.

The working group also spoke with national security and intelligence experts in the U.S. government, who cautioned against making assumptions about the motives or criminal capacities of terrorists. For example, one cannot assume that a terrorist would only be interested in a bioweapon that could be targeted to a particular population rather than one that would cause massive and uncontrollable casualties. The experts also said that classified information can be used to assess risk, but that it has limitations and is not necessarily good at predicting new types of threats.

The working group also examined several published GOF studies to discuss what existing policies and guidelines would apply in those cases and how risks are identified and managed. The group assessed each study to see whether it would fall under the select agencies program or the DURC oversight policies. They also discussed the scientific merit, benefits, risks, and ways to mitigate risk.

Dr. Kanabrocki outlined draft principles, developed by the working group and intended to guide the full Board's deliberations:

1. The NSABB deliberations should focus on defining the problem at hand then include broad consideration of possible solutions.
2. NSABB will consider the potential risks and benefits of a broad range of GOF studies involving influenza, SARS, and MERS viruses in order to identify those that may raise significant concerns that should be addressed.
3. NSABB will consider the risks and benefits associated with alternative research approaches to GOF research to understand whether or not these may substitute for or complement GOF studies.
4. NSABB recommendations will be informed both by data and information about potential risks and benefits as well as values that will guide the evaluation and comparison of these risks and benefits.
5. Uncertainties are inherent in any analyses. NSABB will seek to document important areas of uncertainty in any data or analysis when necessary.
6. NSABB will publicly debate its draft recommendations and describe in its report any dissenting views that may vary substantially from the Board's recommendations.
7. NSABB will consider current USG policies and guidelines, determine whether they adequately address risks associated with GOF research, and make recommendations that are consistent with that determination.
8. NSABB will be mindful that the Board's recommendations and U.S. policy decisions will also influence non-USG funders of life sciences research.
9. NSABB will consider whether there are certain studies that should not be conducted under any circumstances, and if so, articulate the critical characteristics of such studies.
10. Maintaining the public's confidence and trust in life sciences research is critical and must be taken into account as recommendations are formulated.

Next, he presented the working group's preliminary observations and findings:

1. GOF studies entail inherent risks, with the greatest concerns associated with the development and release of a pathogen that is highly dangerous, highly transmissible, and to which a significant proportion of the global human population is susceptible.
2. Evaluation of GOF studies must consider both the risks and benefits.
3. Many different types of GOF studies exist, with many levels of risk. Different levels of risk require different levels of oversight.
4. The U.S. government has a robust policy framework in place to manage risks in life sciences research, but the NSABB must determine whether those policies can adequately

manage risks associated with GOF research involving pathogens with pandemic potential.

5. There are several points in the research cycle at which risks can be managed and oversight applied. It will be important to encourage a sense of shared responsibility for the continued safety, security, and public trust in research.
6. An adaptive policy approach is a desirable way to ensure that oversight and risk mitigation measures are commensurate with the risks associated with the research.
7. Although information associated with scientific research could be misused to cause harm, managing information risks at the publication stage is difficult.
8. Biosafety and biosecurity are international issues requiring global engagement.

The working group's next steps are to continue its deliberations, which will further be informed by the results of the RBA, and to develop draft recommendations to be presented to the Board at the NSABB meeting scheduled for January 7–8, 2016. In March 2016, members of the Board will attend the meeting hosted by the National Academies, after which the NSABB is expected to finalize its recommendations to the USG.

Dr. Stanley commended the working group for its hard work and its significant progress to date. This work will help set up the board for a good discussion of these issues as the meeting proceeds.

NSABB Discussion

Dr. Fitch asked for more specifics on how the working group will incorporate public input into its final report. Dr. Berns replied that the NSABB has public comment sessions at its meetings and also receives written comments from individuals and organizations. An opportunity for further public input will occur at future NSABB meetings and during the meeting at the National Academies in the spring. Dr. Fitch suggested that the working group post the draft recommendations online and allow for a comment period. Dr. Viggiani said the board expects to post its recommendations online prior to its January meeting and in advance of the National Academies meeting. The recommendations are expected to be a major part of the discussion at those meetings.

Dr. Macrina inquired about the group's draft preliminary finding regarding the robustness of the current policy framework for managing risks associated with GOF studies. Dr. Viggiani said that the working group is developing draft work products that will be informed by the discussions at this meeting. These draft work products will include an analysis of the strengths and limitations of current policies pertinent to the GOF issue.

Dr. Berns added that the working group has found that there is already robust oversight of research involving potentially dangerous pathogens. The Board's challenge is to address some of the specific questions associated with GOF issues.

Mr. Park, from the Department of State, suggested that the Board address the scope of the recommendations by noting that the Board is tasked with making recommendations to the U.S.

government. However, it is important to consider whether international actions are needed and if so how these might be approached. Should the U.S. hope that others follow our lead or should the U.S. government directly engage with other governments on the issue? Alternatively, could the issues be addressed through non-federal channels, such as by empowering research institutions?

Dr. Berns responded that the Board's recommendations are meant to apply to the USG. However, international implications are inherent in GOF research. He said one challenge is how to effectively engage the international community. Dr. Stanley noted that the working group had already begun to engage with the international community by including members of the Dutch government and the European Commission.

Break

UPDATE AND DISCUSSION OF RISK-BENEFIT ASSESSMENT FOR GOF STUDIES

Progress Report and Laboratory Risk Assessment

Rocco Casagrande, Ph.D.
Principal Investigator and Managing Director, Gryphon Scientific

Dr. Casagrande described that he and his colleagues would provide an overview of the RBA approach, explain how the RBA approach aligns with the NSABB framework, and provide progress reports on biosafety and biosecurity risk assessments and on the benefit assessment.

The RBA involves three tasks, each of which requires a distinct data collection and analysis:

- Quantitative biosafety risk assessment
- Semi-quantitative biosecurity risk assessment
- Qualitative benefit assessment

This makes it challenging to compare risks and benefits. However, this approach will produce more than enough data to enable comparison of benefits and risks for particular GOF experiments and phenotypes.

The RBA approach is intended to align well with the NSABB framework. However, the benefit analysis is largely qualitative, because there is too little data to do a quantitative analysis. Gryphon will present the barriers that would need to be overcome in order for specific benefits to be be realized.

The RBA will focus on the United States but can account for international research. Gryphon's parametric approach to the risk assessment can accommodate variations in laboratory containment features and practices both within and outside the U.S., such as an HVAC system or shower-out procedures for example.

Risks are inherently global, as are the benefits. Gryphon interviewed foreign subject matter experts to understand their perspectives on benefits and is now analyzing how those benefits can be globalized. The analysis will not consider how U.S. policy on GOF research will affect the actions taken by the rest of the world.

The Gryphon analysis is focused on human health and will not include: risks to agriculture, intellectual property issues, or economic impacts. Regarding agricultural risks, the wild-type strains of avian influenza are already so highly transmissible and highly pathogenic among birds, therefore, it would be difficult to identify a GOF study that would make the virus any more lethal to poultry flocks.

The quantitative biosafety risk assessment includes three components:

- Probability of an infection occurring outside of containment
- Probability of an outbreak escaping local control
- Risk of an outbreak causing a global pandemic (includes estimates of the severity and extent of the outbreaks)

Gryphon will analyze the probability of a pathogen escaping containment by considering containment methods, the types of accidents that could result in a loss of containment, and the risk that an accident could lead to an infected individual, and the risk that the pathogen would spread locally or globally. The models take into account the fact that some outbreaks will extinguish either due to control measures or to stochastic forces. When an outbreak does not self-extinguish, Gryphon will estimate the consequences globally and locally, using a nested susceptible/exposed/infectious/recovered (SEIR) model that accounts for the potential for spread and the potential to control the outbreak in various regions around the world. The overall risk is calculated by combining the risk calculations from the analysis of each of these components..

Gryphon will present the biosafety risk analysis results as a list of potential GOF outcomes and the research conditions that are expected to significantly increase the risk of an outbreak. As a purely hypothetical example, an experiment that creates a strain of human-transmissible influenza virus that can overcome protective vaccination would significantly increase risk of an outbreak, because the virus is more likely to cause an infection once it is outside of the laboratory; the resulting outbreak could potentially lead to more cases and deaths than wild-type strains.

The RBA will analyze, for each of the pathogens listed in the NSABB's framework, how the various phenotypes affect the probability that a laboratory incident leads to an escape from the laboratory and subsequently escape from local control.

Dr. Layton asked whether the analysis is looking at a change in phenotype risk in combination or individually. Dr. Casagrande said the analysis could do both, but will begin by looking at the individual phenotypes. Gryphon will consider a variety of possible scenarios. For example, they would calculate risk when the pathogenicity of a phenotype decreases, but transmissibility increases. For each phenotype, the analysis will consider the likelihood of escaping local control. Dr. Casagrande noted that the consequences of some phenotypes, such as enhanced mortality, are

easier to predict than, for example increased transmissibility, which is an important driver of the risk that outbreaks escape local controls.

Professor Wolf asked what assumptions Gryphon was making about a laboratory's biosafety level (BSL) and the regulations the laboratory is following. Dr. Casagrande said his team is making as few assumptions as possible. They are trying to model all of the components of containment and health monitoring procedures that they are made aware of, through their literature searches and visits to laboratories. The analysis will allow them to consider different scenarios e.g, What if there is no shower-out protocol? Or what if there is no redundant HEPA filtration of the exhaust?

Gryphon has examined previous risk assessments and has supplemented the information with incidents particular to GOF research to identify the most common and the riskiest laboratory accidents that could lead to loss of containment.

Dr. Grant asked about biosafety in field stations, both domestically and internationally, where physical biosafety containment features may be less sophisticated. Dr. Casagrande said that while the types of GOF experiments being analyzed are not typically performed at field stations, scenarios where wild-type specimens are handled are being considered to develop a baseline risk assessment for particular scenarios. Fault tree analysis would allow examination of the critical nodes that significantly affect risk. Gryphon expects to provide the board with a list of safety features that critically affect risk if they are either absent or present. The idea is to identify which safety measures are important, so that they can be factored in when calculating the risk of an accident.

Dr. Stanley asked what data are available regarding animal bites and flu. Dr. Casagrande said Gryphon's current analysis will examine that feature. From their research so far, it appears that the greatest risk is not from the laceration caused by a bite, but from the individual's failure to decontaminate the affected area properly, leading to self-inoculation.

Gryphon will model a variety of ways that an infection can reach the community:

- Unnoticed infection of a laboratory worker, so that infection control protocols are not implemented
- Contamination of a laboratory worker who infects self or others outside the laboratory
- Release of an infectious aerosol into the environment
- Animal escapes, including an animal escaping some containment features and resulting in infection of workers outside the protected area

Dr. Casagrande noted that the risk of an infected animal accidentally escaping a laboratory to the outside is miniscule, but it is important to look at escape from containment within the lab and the possibility of an animal being deliberately removed.

Dr. Casagrande presented results from the modeling of the initiation of an outbreak that assumed a loss of containment due to contamination on the hand of a laboratory worker. The model considered the probabilities of both self-inoculation and infection by the worker and infection of others outside the lab or worker's household.

Dr. Casagrande was asked what data regarding the escape of viruses from laboratories and the ensuing consequences were considered in the analyses. Dr. Casagrande said that Gryphon had searched every report they could find on laboratory accidents and extracted that data, only some of which was in the public domain, including previous risk assessments. He noted that historical data could provide the types of incidents to be modeled, but that empirical data are still needed to provide quantitative data about infections.

Dr. Dixon raised the importance of distinguishing between the risk of a breach and the risk that the breach would result in an infection, noting that reports of breaches of primary containment involving bacteria reported very few infections, with no secondary transmission to the public.

Dr. Casagrande indicated that he did not yet have the analogous results on the spread and consequence of viruses given the current stage of the modeling, but said Gryphon's models will explicitly consider the possibility of a release from containment and whether the release leads to an infection and subsequently a local or global outbreak. He added that Gryphon is looking at all available data from historical incidents and from other epidemiological events, but noted the difficulty in making generalizations based on events that are very rare.

Dr. Layton asked whether results on modeling of worker infection as a result of a laboratory accident would be presented. Dr. Casagrande said they do not have that analysis at this time.

Dr. LeDuc asked whether Gryphon will consider upstream issues, such as worker training and organizational leadership. Dr. Casagrande said that his team has spent a lot of time researching human failure and human reliability assessments, mostly from the nuclear power and chemical engineering fields. However, there is not enough data in the life sciences to give a quantitative assessment of how much training would be required to reduce the chance that a worker would fail to follow protocol.

Mr. Park asked about the range of uncertainty that exists in the models and suggested that information about the drivers of risk and where large uncertainties remain could inform a biosafety research agenda. Dr. Casagrande said that the model would describe where the greatest uncertainty and risk lie and said that Gryphon wants to build a model that is flexible enough to answer many questions, including questions that might have not been anticipated today. He noted that there is a lot of variability in the data underlying the assessments, but that Gryphon will list the assumptions it made while building the model, so that the model can be improved as new information becomes available.

From Gryphon's assessment of the data on the human health consequences of outbreaks of avian influenza, it became clear that there are too many unknowns to predict accurately how an avian virus with new properties would impact humans. If the strain being modeled is contagious among people, the analysis will focus on modeling the human aspect of an outbreak; the assumption being that spread through human-to-human contact is more likely than bird-to-human routes. If not human transmissible, ranges of zero to one thousand human cases and a fatality rate of zero to fifty percent will be considered, based on historical data on outbreaks involving wild-type virus.

Dr. Stanley asked how risk would be modeled for scientists who are working in the surveillance field, who may have no knowledge that they are handling a highly pathogenic virus. Dr. Casagrande said that data to allow them to model the evolution of the strain after it is released do not exist. Also, in the case of bird flu, there are too many variables to predict how readily a bird flu virus would spread among birds. Also the Gryphon model focuses on an outbreak that begins in the laboratory; Gryphon has not assessed field activities. If the specimen comes back to the lab, Gryphon can model that part of the risk.

Dr. Berns asked how the potential risk in a field situation compares with that in a highly regulated laboratory environment. Dr. Casagrande said that fieldwork does not include GOF research; there is no manipulation of pathogens to enhance their phenotypes. Dr. Berns said it would be important for the board to know what the gain in risk is, and with what other scenario it is being compared.

Dr. Casagrande said the team's charge was to focus on the laboratory, where they are comparing manipulations that would enhance a pathogen's characteristics against manipulations that would not. They are not examining risk that could occur in the field and health care situations. A wider investigation would be informative, but is not part of Gryphon's investigation.

Dr. Hammarskjöld said that there is very little information on human-to-human transmission in avian flu. Dr. Casagrande agreed, saying Gryphon's assessment uses empirical data where possible. Gryphon uses a parametric approach where data is insufficient to attempt to predict the degree of increased risk if a phenotype is manipulated to a particular degree. This is supposed to be a prospective model that can be used even with scenarios that have never occurred. If an avian strain becomes human transmissible and is slightly less transmissible than the 1918 flu, the model would predict one level of risk; if the strain became more transmissible than the 1918 flu, the model would predict a higher level of risk.

The next step is to model loss of local control after a pathogen has escaped from the laboratory and causes an infection. Gryphon will draw on a branching process model developed at the University of California, Los Angeles. This is a stochastic model in which each case creates a number of new cases based on a probability distribution with parameters R_0 and k where R_0 represents the average number of new cases each infection generates and k reflects the variation in infections among individuals. An R value of less than 1 predicts that the epidemic will not spread out of control, because there are few new infections. Low k means high variation; high k means low variation. Low k is appropriate for MERS and SARS, because most human infections generate no secondary cases, but some generate a very large number. Higher k is appropriate for flu, which is less variable.

This branching process model captures a crucial feature of outbreaks, which is that many result in very few infections. The model considers various control measures that might be implemented early in an outbreak. It takes into account factors such as how quickly controls are put in place after an infection occurs and how transmissible the pathogen is.

In response to questions from Board members about whether the modeling would account for variable factors such as population density or susceptibility, or the duration of infection, Dr.

Casagrande explained that the branching process model is not a network model, but that many variable factors could be captured by varying the k and R values, which would be based on epidemiological data. He noted that the MERS outbreak had low k values because a few individuals infected many people..It is not clear whether those individuals transmitted the pathogen because of the nature of the pathogen, their behavior, the people they contacted, or other reasons. Gryphon did consider using a network analysis but felt that there were too many uncertainties and that the numbers would have no real data behind them.

To estimate the extent and severity of outbreaks that escape local control, Gryphon will use the HHS Biomedical Advanced Research and Development Authority (BARDA) Interactive Influenza Model, which the Centers for Disease Control and Prevention (CDC) uses to predict how different responses can mitigate flu outbreaks.

All of the SEIR models assume that the population is demographically well mixed (children, adults, and the elderly) and takes into account contact rates in households, schools, and workplaces. The model was developed for the United States, but Gryphon will run the model on several global regions to estimate the global consequences of disease. The analysis takes contact rates under different settings (e.g., schools or work) into account and will include regional data on vaccination rates, total population, and age. The model can predict the extent and the consequences of an outbreak and can account for variables such as mortality rate and viral resistance.

Dr. Berns asked how flu immunizations affect mortality. Dr. Casagrande said the model would allow Gryphon to take into account the effectiveness of a vaccine, the amount of vaccine available, and the number of people who get vaccinated.

Dr. Patterson asked whether the model could help the Board develop a policy that will be effective in laboratories whose biosafety profile and capacity to respond to an outbreak differ. Dr. Casagrande said that the model takes into account variables such as the specific protections the laboratory has in place. He said he approached the question by considering the potential for the proliferation of GOF research. Based on analysis of publications, there are about 40 groups in the United States that could undertake GOF research, although that may be an underestimate. Nationwide, there are approximately 300 BSL3 laboratories and fewer than ten BSL4 laboratories. Gryphon also did case studies on SARS and flu to see whether research had proliferated and to what extent. That information will help predict how many new laboratories might begin GOF research in the future.

Biosecurity Risk Assessment
Kavita Berger, Ph.D.
Scientist, Gryphon Scientific

Dr. Berger said that the security risk assessment examines malicious actor incidents described in open source literature. A review of these incidents helped identify the actors' motivations and capabilities. The assessment also includes an evaluation of security governance. Gryphon used the information to develop case studies for epidemiological modeling.

Most historical incidents involving laboratories in the United States involve animal rights activists who released infected animals. There are instances of contamination of laboratory facilities, release of information for personal gain, destruction of property, acts of personal revenge, and theft of information. The acts were carried out by organized criminals, foreign governments, and people inside laboratories who were working alone.

Dr. Berger said the analysis includes every incident they could find in open sources, whether inside or outside the United States and whether or not the facility had received government funding. Most of the incidents were hospital-related.. A board member said it would be valuable to know which of these incidents involved facilities with U.S. government funding since those laboratories will also be required to follow any regulations the USG establishes.

Dr. Berger next discussed governance and implementation—the "defense" part of biosecurity—in light of the types of malicious actor threats discussed earlier. The analysis included three levels of security; non-select agents in BSL-3 labs; select agent labs; and, the most secure being a Tier 1 select agent laboratory.

To develop the security scenarios, Gryphon began with the possible malicious actor, then examined the actor's opportunity to acquire a pathogen and the malicious acts that were probable. Their analysis confirms that an insider is the most likely to cause a biosecurity breach, with possible breaches including removal of an infected animal or pathogen from the laboratory.

Gryphon also examined biosecurity risks associated with dual use information stemming from GOF studies and which GOF phenotypes would provide a unique advantage to a hostile actor. Gryphon is analyzing the published literature to determine what information already exists in the literature and will compare the information that has yet to be published with the motivations and capabilities of adversaries.

Benefit Assessment
Corey Meyer, Ph.D.
Senior Analyst, Gryphon Scientific

The goal of the benefit assessment is to identify the unique benefits of GOF research and to identify whether GOF studies can uniquely, more effectively, or more rapidly address gaps in scientific knowledge and public health than alternative approaches.

The benefit analysis will enable evaluation of individual experimental approaches within each GOF phenotype, because different approaches might have different risks and benefits. The analysis will be structured to enable comparison of the risks and benefits associated with each GOF approach.

The risks of an experiment depend to a considerable degree on the viral strain and the specific experimental manipulation. The benefits derive largely from the experiment's outcomes. The risk analysis is quantitative; the benefit assessment is largely qualitative.

Dr. Meyer explained how Gryphon is assessing the benefits of GOF research by reviewing the influenza and coronavirus literature, to describe the GOF research in each field and identify alternative experimental approaches that could provide similar scientific information. Gryphon collected this literature into a set of general experiments, each characterized by the experimental approach, the virus strains that can be used for that experiment, and the scientific outcomes.

Dr. Meyer outlined the approaches Gryphon is taking to evaluate the public health benefits of GOF research to improve vaccine yields or identify genetic markers for the phenotypic properties of concern. The latter helps assess pandemic risk and develop pre-pandemic vaccines. The former shortens production times for strain-specific vaccines.

One aspect of the benefit assessment is determining how many lives could be saved when a vaccine can be deployed earlier. However, not all benefits can be quantified.

By using these examples, Dr. Meyer illustrated how Gryphon proposes to present the public health benefits of each GOF study.

Dr. Grant asked Dr. Meyer to explain what she means by qualitative benefits. Dr. Meyer said that Gryphon has derived this information from a review of the literature and interviews with scientists and subject matter experts, including translational experts who apply the research to public health. The team has talked to scientists involved in vaccine development, manufacture, and purchase. Gryphon will provide an appendix listing all those who have been interviewed.

Gryphon also did an additional analysis that considered how the loss of public trust could affect the scientific enterprise. Researchers looked at historical incidents that could lead to a loss of trust, such as incidents involving nuclear power.

Public Comment

Megan Palmer, Ph.D., Center for International Security and Cooperation at Stanford University, noted that there is little primary data available for the risk-benefit analysis to draw from. It will be important to identify assumptions made and uncertainties in this analysis. She encouraged the Board to consider ways to evaluate the effectiveness and impacts of its recommendations and policies in this area. The DURC policy went into effect last week, but how will its effects be measured? She also asked the Board to consider showcasing and drawing lessons from other fields that have successfully managed risk.

Marc Lipsitch, Ph.D., of the Harvard T.H. Chan School of Public Health, stated that he did not consider the existing framework of oversight to be sufficiently robust. He was concerned that the DURC process did not flag research with potentially pandemic pathogens as a separate issue until biosafety accidents happened at prominent laboratories, and public reaction forced the issue. The current framework for H5N1 and H7N9 has flaws, according to Dr. Lipsitch. Much of the oversight is provided by the institutional biosafety committees (IBCs). These committees may lack the proper expertise to review this research. The IBCs often lack the expertise to manage global health risks. Another issue is that IBC members come from within the institution

that receives the funding; they are not disinterested parties. They see their role as supporting the research, which may explain why they accept the claims of investigators. Also, IBCs make no attempt to quantify risk, which they should. Finally, Dr. Lipsitch said that the scope of the NSABB's deliberations is too narrow because it only applies to federally funded research.

Working lunch

THE ETHICAL LEGAL AND POLICY ISSUES ASSOCIATED WITH GAIN-OF-FUNCTION STUDIES

Susan Wolf, J.D., Moderator
McKnight Presidential Professor of Law, Medicine, and Public Policy, Faegre Baker Daniels Professor of Law, Professor of Medicine, University of Minnesota Law School

Professor Wolf noted that the Board will need to consider many ethical issues as it develops its policy recommendations. The following questions should be among those considered during the presentation and discussions:

- What values and decision-making frameworks should NSABB consider in moving beyond the RBA in order to formulate policy recommendations on GOF studies involving pathogens with pandemic potential?
- Is there GOF research that should not be funded and conducted? If so, what are the features of such studies, and what considerations should guide the identification of GOF studies that might meet such a designation?
- After considering risks and benefits, what policy options or oversight strategies might the NSABB consider in generating recommendations to the U.S. government on the funding and conduct of GOF studies involving pathogens with pandemic potential?

Gain of Function Research: Ethical Analysis

Michael Selgelid, Ph.D., Presenter
Director, Center of Human Bioethics; Professor of Bioethics, School of Philosophical, Historical and International Studies, Monash University, Australia

Dr. Selgelid explained that he has been commissioned by the NIH to write a white paper to help inform NSABB's deliberations. His paper will consist of a literature review of the ethics of GOF research; identification and analysis of frameworks for making decisions about outcomes entailing risks, benefits, and uncertainty; and development of a decision-making framework to assist policy decisions, particularly regarding funding of GOF research. This is a preliminary report as Dr. Selgelid had only recently begun the project.

The literature review so far has shown that there have been only about ten papers specifically on the ethics of GOF research that have been authored by ethicists. When he broadened the search to include all studies that address the question of ethics of GOF, Dr. Selgelid identified approximately 45 papers. The most relevant literature concerns the ethics of dual use research and the ethics of biosafety.

The GOF debate is an ethics debate because it must address what *should* be done. There has been a shift in focus on dual use research to include biosafety as well as biosecurity. There have been worries about the conditions under which GOF work was conducted, as well as concerns that the research will proliferate to laboratories that maintain less safe conditions. There are also concerns about the magnitude of the risk of some of the studies done and about measuring risk accurately.

Increased transparency and broader community engagement and consultation are important. The conversation has been taking place among scientists, but it should be made more public. There have been calls for an objective, independent RBA.

Regarding risks, there also has been an appeal to the principle of doing no harm. There are concerns about imposing risks on others, including the general public. Other discussions encourage researchers to minimize risks by choosing approaches that are less risky, and individuals have called for quantification of the risks and weighing the risks against the benefits.

Regarding benefits, Dr. Selgelid noted the debate over whether key public health questions were answered with previous GOF studies, such as the initial H5N1 ferret studies. How translatable was the ferret study to humans? Has there been beneficial change to policy or practice as a result of the debates that have arisen?

There is also debate about whether GOF research is the best way to answer key questions and achieve public health goals. Are there less risky ways to do the research? In the literature, concerns have been expressed about stalling important areas of research as a result of the pause in research funding. There have been questions about the value of scientific knowledge: Is knowledge valuable for its own sake or for the sake of public health?

It should not be assumed that all GOF research should not be done. As with dual use research, only a subset of GOF research is of concern and may require additional scrutiny or oversight. Some potential pandemic pathogens are more dangerous than others and require an adequate governance system to deal with them, whether or not they are part of a GOF research project.

The values at stake in GOF research largely concern public health, including the number of lives saved or lost and the well-being of individuals that can be improved or compromised. Security is an important value, as are scientific advancement and academic freedom (i.e., freedom from interference). However, academic freedom does not require that research be funded. In short, there are many values at stake; the question is how these values should be weighed when they are in conflict.

Some of the hard questions include weighing the risk of causing harm versus preventing it. People might disagree about how to rate the risks versus the benefits, and there are no facts about how these values should be weighted. However, it might make sense to look at the aggregate number of lives saved or lost and the disability-adjusted life years saved or lost. To take into account many more values might make interpretation of the RBA too complex.

There are limitations to even the best RBA. RBAs can be very complex because of the number of scenarios and risk factors that must be taken into account. RBAs rely on assumptions and on uncertain data. Even with the best data, it is not always possible to know whether the benefits outweigh the risks, and there can be disagreement about when the risks outweigh the benefits.

Dr. Selegid reviewed some of the existing decision-making frameworks including their advantages and limitations in different situations. Hybrid or plural ways to make decisions may be required so that the most flexible approach can be taken. The community must be engaged because the risk-taking strategy chosen should reflect the risk-taking tolerance of the people who will be most affected.

Risks, Benefits, and Ethics in Gain-of-Function Studies
Rebecca Dresser, J.D., Panelist (via teleconference)
Daniel Noyes Kirby Professor of Law, Professor of Ethics in Medicine, Washington University in St. Louis

Professor Dresser said that the field of research ethics usually balances the risk to human subjects against the benefits to the public. The Belmont Report, released in 1979, laid out the general ethical principles of human subjects research. Beneficence, one of the principles that underlie ethical research, requires that research risks be justified by potential benefits to society. It raises questions about when risk is justifiable, when it is not justifiable, and how to minimize risk as much as possible.

Other ethical principles include respect for individuals, demonstrated by giving people the freedom to decide whether to accept research risks after giving them the information to make that decision; that is, informed consent. There is also the principle of justice, which involves a fair distribution of research risks and benefits among individuals and groups.

The question of respect and justice in risk exposure is an issue to explore. Should there be a requirement to give notice of the potential risks of GOF research to laboratory workers, clinicians who would care for those affected, others present in the facilities, those who are in close contact with any of these groups, or the general public? What about requiring researchers to obtain the consent of certain of these groups? Should people in these groups be allowed to opt out?

Professor Dresser noted that the general public might be the most difficult to inform - and from whom should one obtain consent? Public consent is usually obtained by including members of the public on various committees, such as human subjects committees and institutional review boards. When it comes to GOF research, would participation on these various committees be sufficient public engagement, or would more be needed? What level of transparency is required? How could scientists supply the level of education that might be necessary for the public to adequately evaluate the risks and benefits? Are citizen panels or deliberative polls required?

While there are many questions about exactly how to obtain true informed consent, Professor Dresser said that broad participation in RBA decision-making will allow more perspectives to be represented and the better the final decision will be.

Researchers have faced these questions before; for example, in the debate about xenotransplantation studies in humans; decisions ,about implanting an artificial heart powered with plutonium; and with recombinant DNA experiments. Xenotransplantation studies in humans were mostly allowed, but they included an informed consent for people who received animal tissues. However, primate-to-primate transplantation was not allowed, because there were insufficient safety data.

The nuclear-powered artificial heart was not approved, because it was estimated to cause one additional case of cancer per every 7,200 cases of cancer reported that would have occurred anyway. There were also worries about terrorists obtaining the material and concerns about what should be done with the material when the recipient died. Scientists concluded the heart should not be implanted, because of risks that extended to individuals other than the recipient

Recombinant DNA research was approved and allowed to move forward, on the condition that certain public safety measures be imposed.

Professor Dresser noted that the committees that considered the transplant and artificial heart issues were called upon to balance the benefits to the people who needed the organs against the public health risks. Having an identifiable victim can affect the moral reasoning that goes into making such decisions. However, that is not so true of GOF research, where the potential benefits and harms will be expressed in statistical terms.

In addition to considering which research should not be done and which research could be done only under close scrutiny, it would also be helpful to consider how to develop safer alternatives to risky research. Professor Dresser provided a literature citation to an article in which the authors describe creative ways to find alternatives to GOF research.

Ethical and Policy Issues in Selecting Oversight Frameworks for Gain-of-Function Studies
Eric Meslin, Ph.D., Panelist
Director, Indiana University Center for Bioethics; Associate Dean and Professor of Bioethics, Indiana University School of Medicine; Managing Director, Center for Law, Ethics, and Applied Research in Health Information

Dr. Meslin said that his talk would focus on Question 3: “After considering risks and benefits, what policy options or oversight strategies might the NSABB consider in generating recommendations to the U.S. government on the funding and conduct of GOF studies involving pathogens with pandemic potential?”

The Board is being asked some framework questions, which are really questions of research governance. The regulations, principles, and standards of good practice that exist to promote a policy come down to whether things should be banned, permitted, or promoted. Dr. Meslin said

that the Board is likely falling in the middle area (permitted or enabled as opposed to banning versus encouraging).

When research is enabled, researchers need to know the rules, and there must be some oversight of the research (governance) to assure compliance with the rules.

One goal of governance is to protect human subjects and laboratory workers in many types of research, including clinical trials and genomic studies. Institutional review boards, data safety monitoring boards, biosafety committees, and other groups provide oversight. These governance models were developed as a result of the Belmont Report and other documents meant to protect human and animal subjects.

Another goal of governance is to enable high-quality, benefit-maximizing research using clear rules. The type of governance mechanism depends on the study but can include scientific peer review, journal peer review, and appropriations by government sponsors. In order to encourage high-quality, benefit-maximizing research, it is necessary to select the appropriate governance mechanism.

A third goal is to ensure public health and safety, both domestically and internationally.

Dr. Meslin ended his presentation with a list of principles, values, and norms. The challenge is to choose the criteria that will best animate the policy the Board recommends. The substantive principles, values, and norms:

- Non-maleficence
- Precaution
- Proportionality
- Reciprocity
- Fair benefits
- Academic freedom
- Contribution to knowledge
- Reputation, status

The procedural principles, values, and norms:

- Prior agreements
- Responsiveness
- Transparency
- Uniformity of implementation

He summarized his points as follows:

- Different governance goals and different types of governance lead to an incommensurability problem.
- GOF governance emphasizes public health, unlike the biomedical research governance environment, in which minimizing risk to human subjects is the primary emphasis of governance.
- Conflict versus confluence of interests should be acknowledged.

NSABB Discussion

Professor Wolf asked whether there is research that should not be done. Dr. Selgelid said that research that involved developing a pathogen as lethal, contagious, and untreatable as smallpox may be an example of a study should not be conducted, adding that it is not clear what the benefits would be and the outcome could be very dangerous if successful. However, he might make an exception if the research were done as classified research.

Noting that it was difficult to make a general principle to answer this question, Professor Dresser said research should not be done when the risks are high and the benefits are not. It is also important to get public input on these questions. If the reaction is negative, then the research should not be carried out.

Dr. Meslin said that it is difficult to make a blanket statement about banning any particular type of research, but he agreed with the answers Dr. Selgelid and Ms. Dresser provided and would add that a study that, at the time, had no compelling public health benefit should not be carried out.

In response to the smallpox example, Dr. Layton said that an experiment in which avian flu was made more transmissible could be worse than GOF work with smallpox. Dr. Selgelid said that the difference is that along with the concerns expressed, there are arguably good reasons for doing the influenza research. However with his smallpox example there are arguably good reasons for concern, but there not many compelling public health reasons for doing it. Akin to Dr. Meslin's point, the greater the risk the more compelling the problem it addresses needs to be.

Dr. McDade asked about informed consent for the public. Is the public the local, national, or international public? The entire public cannot give informed consent en masse, but consent might involve giving the public information. Would that address some of the ethical concerns?

Professor Dresser said that if an accident or security breach occurred and the public suffered, it would create a lack of public trust in research. The Board should consider developing recommendations for how different groups of people should be informed of GOF research. This would include hospital staff, laboratory staff, and hospital visitors. Those groups should be invited to give input on the work. It is difficult to give meaningful information to people who are more distant from the hospital and laboratory.

Dr. Meslin said that he would not use the term informed consent. The issue is really about suggesting that researchers communicate better with the public. There are already 15 to 20 examples of the public being misled or misinformed about a scientific activity, eroding trust. Researchers must engage with the community.

Dr. Selgelid said that it is important to have policies that reflect the values and risk-taking attitudes of the public. Developing those policies will require that researchers find out what those values and attitudes are. It would not be practical to get everybody in a community to agree on a particular magnitude of risk, but there has to be a democratic way to align the risk with the overall desire of the community.

In response to Professor Wolf's inquiry about how empirical ethics could inform the Board's recommendations Dr. Meslin said that the scientific community has been struggling for the past 40 years to see whether IRBs protect the rights and welfare of human subjects. The Board should build an evaluation aspect into their recommendations and then evaluate how well the framework is working to protect public welfare and promote good science. If there is no way to evaluate the framework's impact, there is no point to having the framework.

Professor Wolf thanked the participants and said that it was valuable to hear what could be derived from past frameworks, such as the Belmont Report. The discussion gave the Board a lot to think about.

Dr. Stanley agreed and said that the idea of developing a framework that can be evaluated in terms of how well it is working is something the Board will be discussing.

PUBLIC COMMENTS

David Spiro, Ph.D., of the National Institute of Allergy and Infectious Diseases (NIAID), asked a question on behalf of a NIAID grantee: Given that we do not know how transmissible avian viruses are in humans, how useful are the models of global spread presented by Dr. Casagrande?

Dr. Casagrande said the purpose of the RBA is to look at scenarios and phenotypes that may be reasonably anticipated to be conducted and then to provide data on the risks and benefits. He noted the risks and benefits associated with work in animal model systems are difficult to separate since model systems are chosen based on the translatability of observations and benefits to human health.

Mr. Park said that much of the discussion centered on whether the benefits of research would exceed the risks. He asked whether there is some limit to the amount of risk that would be tolerated, regardless of whether the benefits exceed the risk.

Professor Dresser said that Nuremberg Code and the Helsinki Accords hold that if research would kill one person, the project should not be done, even if the benefits are very great. Professor Wolf cited several other projects that have not gone forward because the risks outweigh the benefits. It would be instructive for the Board to examine those instances.

Dr. Grant said that she was intrigued by the notion of looking at alternatives to GOF experiments before going ahead with potentially risky experiments. She asked whether there is an ethical obligation to look at alternatives first. Dr. Meslin said that there is a long history in bioethics of having a moral obligation to use the least invasive, painful, or undignified intervention to obtain a given benefit. Identifying the appropriate option does require a comparison of which course of action would be best. This is a moral question as much as a scientific question.

Dr. McDade asked whether the Board should assume that every GOF study has to be looked at from an ethics point of view. There may be too many gates for research proposals to go through.

Is there a way to determine when researchers can go directly to questions of biosafety and biosecurity?

Dr. Wolf said that it is important to develop a culture of responsible research among investigators involved in all kinds of research, not just human subjects research.

Dr. Selgelid said that the task is to delineate GOF research of concern; that is, research that poses an extraordinary risk. Dr. Berns said it is important to have transparency about the risks and benefits of the research to maintain public confidence.

Another participant commented that there are various levels of informing the public, ranging from giving them information, to asking for input, to asking for permission.

Dr. Wolf asked whether the RBA would consider what policies are already in place for biosafety to aid the Board in its evaluations.

Dr. Casagrande said that the RBA will attempt to capture existing biosafety policy and regulations in so far as they are embodied in a physical system or human or laboratory practice.

Dr. LeDuc emphasized that the Board should consider recommendations that are applicable as far upstream in the research continuum as possible, noting that it becomes more difficult to influence what research is done and more so what information is released after the work is done.

Dr. Casagrande added that his team has visited a number of laboratories doing GOF research. Some have a strong culture of biosafety and good working relationships with local communities. Those factors are not easily captured in the model, but they can make a difference in safety. While many nuances will not be captured in the model, they will be scrutinized in the best practices study.

Dr. Endy said that there are a limited number of laboratories currently doing GOF work, but that number could greatly expand in the future. Human error is a major concern in these laboratories and may require researchers to build a new cultural framework that emphasizes safety.

Dr. Resnick said that there is no simple solution, because the laboratory environment is complex. The Board should develop policies that can be changed and adapted as necessary.

In response to a question about how current structures that incentivize curiosity driven research and publications with “surprise value” might apply to the GOF discussions Dr. Meslin noted that there has been some shift away from incentivizing individual investigators and curiosity driven research in general. He suggested that the idea that work should have impact beyond the interest of the researcher is taking precedence and that any model that works will have to include the funders who largely influence this landscape.

CONCLUDING REMARKS AND ADJOURN
Samuel L. Stanley, M.D., Chair

Dr. Stanley said that he was grateful to the NSABB working group, which has made significant progress.

The work by Gryphon Scientific has also made progress and sparked a vigorous discussion. He was pleased that some boundaries were set by focusing the RBA on human disease.

The ethics discussion led by Professor Wolf was valuable and generated important discussion. As the Board continues to deliberate, one question that has been raised is how to create something that will have effects that can be measured. Another issue was the educational potential of its recommendations and the importance of engaging the scientific, policy communities, and the public (domestically and internationally) on laboratory safety and security.

Dr. Stanley encouraged members to review the documents they have received and to make suggestions for the agenda of the next Board meeting.

The next steps are for the working group to continue its deliberations. Gryphon will complete its work on the RBA and present it to the working group in November. The full Board will next meet in January 2016. The National Academies will hold its meeting in March 2016, when the Board's preliminary findings and recommendations will be discussed. The Board will finalize its recommendations sometime after the National Academies meeting.

Dr. Stanley adjourned the meeting at 2:10 p.m.