National Science Advisory Board for Biosecurity

National Institutes of Health
Bethesda, MD
May 24, 2016

Meeting Summary

Purpose of Meeting and Background

The members of the National Science Advisory Board for Biosecurity (NSABB), including the Working Group on Evaluating Risks and Benefits of Gain-of-Function Studies and the ex officio members of the NSABB, met to discuss and finalize the NSABB Draft Report *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research*.

Welcome and Introductions

NSABB Chair Samuel L. Stanley, M.D., Stony Brook University, welcomed the attendees and reviewed the history of NSABB's consideration of the gain-of-function (GOF) issue. While there are legitimate scientific and public health reasons for conducting GOF studies, certain studies, particularly those that could generate pathogens with pandemic potential, have raised concerns. The debate has evolved to focus on biosafety and whether such research should be funded, and if so, how they can be safely conducted.

In October 2014, the U.S. government asked NSABB to address the issue of GOF studies. Certain GOF studies have been paused while the risks and benefits of this type of research are being reevaluated. In addition to six public meetings of the NSABB, this GOF deliberative process has included two public workshops hosted by the National Academies, a formal risk and benefit analysis, and extensive consultations with domestic and international stakeholders.

Dr. Stanley thanked the members of the NSABB working group for their hard work and noted the major order of business for the Board was discussion and finalization of the NSABB's draft report on the GOF issue.

Christopher Viggiani, Ph.D., Executive Director of the NSABB, reviewed the conflict of interest rules and the Board unanimously approved the minutes of the January 2016 NSABB meeting.

Acknowledgement of Service of Departing NSABB Members

Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director of the National Institutes of Health (NIH), thanked the members of the NSABB who were rotating off of the Board for their service and presented them with certificates of appreciation on behalf of the U.S. government. Since the NSABB's founding in 2004, it has weighed in on many challenging and controversial issues, providing valuable counsel not only to NIH but to the entire U.S. government. NSABB's advice and recommendations have led to tangible changes in U.S. policy and have informed discussions internationally.

The Gain-of-Function Policy Development Process to Date and Next Steps

Gerald L. Epstein, Ph.D., Office of Science and Technology Policy (OSTP), summarized the process of policy development for GOF research. Dr. Epstein is an ex officio member of the NSABB and will be coordinating the government's policy development process for GOF research, which will involve consideration of NSABB recommendations.

The challenge for the government is to reliably identify and—where necessary and possible—mitigate risks while protecting scientific autonomy, discovery and innovation, public health, national security, and other critical interests.

This is the second round of policymaking related to GOF research. In 2011–2012, NSABB was asked to review and provide advice on the appropriate communication of two manuscripts reporting studies that resulted in the generation of highly pathogenic H5N1 avian influenza viruses that were transmissible between mammals via the respiratory route. NSABB found legal and logistical barriers to redaction and ultimately recommended publishing revised versions of the manuscripts in unredacted form.

In mid-2014, NSABB returned to the issue of GOF research, prompted by a series of high-profile laboratory biosafety incidents. The biosafety lapses did not involve GOF experiments, but they raised concerns and reemphasized to the importance of assessing the potential risks and benefits associated with GOF research at the time funding decisions are being made. The greatest concerns centered on GOF studies that involved the generation of pathogens that have the potential to cause pandemics—particularly via respiratory transmission. This led to the launch of the U.S. government GOF deliberative process in October 2014 and the accompanying funding pause on certain categories of GOF research involving SARS, MERS, and influenza.

NSABB is the official federal advisory body for providing advice on oversight of DURC, which includes the types of GOF research that have raised concerns. The Board operates under the Federal Advisory Committee Act, which means it has requirements in areas such as transparency and receiving public comment. Another key voice in the discussion is the National Academies, which convened two workshops to solicit broad stakeholder input and help inform NSABB's deliberations.

NSABB formed two Working Groups – one focused on advising the design and conduct of risk and benefit assessments of GOF studies, and a second focused on evaluating the potential risks and benefits and developing recommendations on funding and conduct of GOF research. An in-depth risk and benefit analysis of GOF research was conducted by Gryphon Scientific, an independent contractor. The final step in the deliberative process is for NSABB to formally adopt and transmit policy recommendations to the U.S. government.

Once policy recommendations are made, the White House will lead a U.S. government policy development process on the issue of GOF research that will consider the NSABB's recommendations as well as all the information generated and feedback received throughout the deliberative process. This policy would supersede the ongoing GOF funding pause. Dr. Epstein noted that public comments will still be accepted even after formal NSABB recommendations are adopted.

Review and Discussion of NSABB Draft Report

Presentation from the NSABB Working Group

Dr. Joseph Kanabrocki, Ph.D., C.B.S.P., Co-chair, NSABB Working Group, provided an overview of the draft report.

The working group focused on four major areas:

- Evaluation of potential risks and benefits of certain GOF research, which was informed by the risk and benefit assessment conducted by Gryphon Scientific. The report, Risk and Benefit Analysis of Gain of Function Research, includes biosafety risk assessment, which is the risks associated with laboratory accidents; biosecurity risk assessment, including assessment of risks related to malevolent use of information; and benefits assessment. The report made it possible for NSABB to understand risks associated with GOF research, the types of studies that are of concern, and the potential benefits of the research, and to consider possible alternative approaches. The risk and benefit assessment was guided by the May 2015 Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research, which set out features and principles to guide the development and conduct of the analysis.

- Ethical issues and decision-making, informed by consultations with ethicists and an Ethical Analysis performed by Professor Michael Selgelid, Ph.D. of Monash University. The ethical analysis reviewed ethical literature on GOF research and proposed a decision-making framework regarding GOF research. Informed by this, the working group identified core values to be considered when evaluating research proposals involving GOF studies and establishing mechanisms for reviewing proposals and making funding decisions.

- Domestic and international policies and guidelines and potential policy options, informed by briefings from experts, examination of literature, and U.S. government documents. This included discussions with overseas partners who are also engaged in discussion of and policy development on DURC and GOF research.

- Perspectives of stakeholders, obtained from NSABB and working group meetings, National Academies workshops, and public comments.

The draft report, particularly the findings and draft recommendations, has been revised extensively based on feedback received since it was first discussed at the January NSABB meeting. The working group welcomed feedback on the current draft from the rest of the Board. The working group's draft report can be found at http://osp.od.nih.gov/sites/default/files/NSABB_Working_Group_Draft_Report.pdf.

The following is a summary of the findings from the working group's draft report.

> Finding 1. There are many types of GOF studies and not all of them have the same level of risks. Only a small subset of GOF research—GOF research of concern (GOFROC)—entail risks that are potentially significant enough to warrant additional oversight.
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> Finding 2. The U.S. government has several policies in place for identifying and managing risks associated with life sciences research. There are several points throughout the research life cycle where, if the policies are implemented effectively,

risks can be managed and oversight of GOF research of concern could be implemented.

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

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

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

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

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

The working group heard many times that GOF research is a broad term that captures many kinds of studies, many of which are not cause for concern. This prompted the group to focus its draft recommendations on the subset of GOF research that has the potential to generate pathogens with pandemic potential, which the group defined as GOF research of concern (GOFROC).

The following is a summary of the recommendations from the working group's draft report.

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

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

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

Recommendation 3.1. The U.S. government should consider developing a system to collect and analyze data about laboratory safety incidents to inform GOF research of concern policy development over time.

Recommendation 4. In general, oversight mechanisms for GOF research of concern

should be incorporated into existing policy frameworks when possible.

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

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

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

The working group provided further recommendations on identifying GOFROC. GOFROC is research that can be reasonably anticipated to generate a pathogen with both of the following attributes:

1. The pathogen generated is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations and
2. The pathogen generated is likely highly virulent and likely to cause significant morbidity and/or mortality in humans.

The working group also developed a list of eight principles that should guide the review and funding decision for GOFROC:

i. The research proposal has been evaluated by a peer-review process and determined to be scientifically meritorious, with high impact on the research field(s) involved.

ii. The pathogen that is anticipated to be generated must be judged, based on scientific evidence, to be able to arise by natural processes.

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

iv. There are no feasible, equally efficacious alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach.

v. The investigator and institution proposing the research have the demonstrated capacity and commitment to conduct it safely and securely, and have the ability to respond rapidly and adequately to laboratory accidents and security breaches.

vi. The results of the research are anticipated to be broadly shared in compliance with applicable laws and regulations in order to realize its potential benefits to global health.

vii. The research will be supported through funding mechanisms that allow for appropriate management of risks and ongoing Federal and institutional oversight of all aspects of the research throughout the course of the project.

viii. The proposed research is ethically justifiable.

The last principle is a reminder that, while many of the ethical values considered by the working group are embedded in the eight principles, broader ethical values must also be considered when reviewing

proposals that involve GOFROC.

The group also offered a proposed process for evaluating and making decisions about proposed research involving GOFROC. The process includes identification of potential GOFROC by the principal investigator and institution proposing the research, and identification and pre-funding decision evaluation of GOFROC proposals by an interdisciplinary, federal department-level panel. If the work is determined to be GOFROC and eventually funded, both the institution and the federal government would have responsibilities for ongoing oversight. The working group also proposed that this evaluation and decision-making process be periodically reviewed by an external advisory body, to inform potential improvements if needed.

Discussion of NSABB Report

The adaptive approach advocated for in Recommendation 3 is similar to the approach taken in the past for guidelines on research involving recombinant DNA. This approach allows the government to adapt and modify the guidelines as more is learned about the topic.

Patrick Fitch, Ph.D., Battelle National Biodefense Institute, thanked various advisors who gave input to the working group on the challenges of running an Institutional Review Entity (IRE), which was required of institutions subject to the U.S. government institutional DURC policy. This led to consideration of whether the government would be able to facilitate the sharing of information about the issues and challenges faced, and decisions made by, IREs. Dr. Fitch proposed additional language to Recommendation 3:

> 3.2. The U.S. government should consider developing a system to collect and analyze data about institutional review entity (IRE) challenges, decisions, and lessons learned, to provide feedback to the IRE community and to inform gain-of-function research of concern policy development over time. Examining such data would provide a better understanding of the effectiveness and consistency of policy implementation in support of local IRE decision-making.

The Board agreed that it is important to have dialogue on how decisions regarding GOFROC are being made. Such information sharing could help IREs make consistent decisions and avoid, for example, a situation in which one IRE concludes that a particular study involves GOFROC or was inappropriate, but the IRE at a different institution does not identify the same or similar research as being of concern.

Other key points of NSABB discussion:

- GOF research encompasses a broad spectrum of pathogens and experiments. The Board considered its charge and determined that the appropriate scope of their deliberations and recommendations was on research likely to generate pathogens with pandemic potential among humans, not animals. This is addressed in the report. However the working group agreed that there is potential research of concern regarding agriculture, food, and animal safety that the current process could provide a template for considering.

- The working group considered whether there were studies that should be banned. In general they found that GOFROC can be funded if considered and conducted appropriately. Rather than

listing particular types of studies that should be off limits, the group chose the principle-based approach reflected in the recommendations, which should be flexible enough to be applied to any research that could be considered GOFROC.

- The review of GOFROC should integrate with the other reviews that take place for any proposed research.

- Appropriate expertise should be applied and consistency should be ensured across reviews for GOFROC conducted by different institutions and government agencies.

- Recommendation 2 was added after the second National Academies meetings. The working group thinks that it is important for an advisory body to evaluate the implementation of policies for oversight of GOFROC. This body could examine the review process and provide recommendations for strengthening the process. This would increase transparency and facilitate continued dialogue.

- The Board's recommendations were primarily developed to guide federal funding decisions. However it seems inconsistent, given the potential risks associated with GOFROC, to limit the government's oversight to government-funded research, leaving other GOFROC to be conducted in the United States without additional oversight. Recommendation 5 would extend equivalent oversight to GOFROC non-federally funded GOFROC, to include U.S. companies doing research domestically and at foreign sites.

- Federal policy alone will not be sufficient to mitigate potential risk; bottom-up approaches that include outreach and education on DURC and GOFROC are important. Scientific societies have important roles to play. Continued engagement with domestic and international stakeholders on the issues should continue.

Several ex officio members of the committee and representatives from federal departments and agencies spoke briefly about their initial, positive responses to the recommendations and applauded NSABB for its deliberative process. In addition:

- Dennis Dixon, Ph.D., NIH, and others noted that the federal department and agencies have developed significant experience identifying and managing the potential risks associated with DURC and could apply this expertise to GOFROC.

- Dr. Epstein reiterated that NSABB's recommendations are advisory and that some of them will translate easily into policy and others will not. Conversely, NSABB is not bound by the limits of the policymaking process and should not restrict its recommendations to those which will be easily accomplished.

Public Comment

The public was welcomed to submit comments in person or via the internet.

George Rudy, member of the Containment Lab Community Advisory Committee of the city of Fredrick, Maryland: Public health officials at the state and local levels should be explicitly encouraged to be involved in the GOFROC process. Foreign companies that operate in the United States should be

included in Recommendation 5.

Tyler John, NIH Department of Bioethics, speaking as a member of the public: NSABB and policymakers might consider a policy requiring GOFROC researchers to obtain an independent assessment of risk. The cost of this assessment would be part of the cost of the research project.

Rocco Casagrande, Gryphon Scientific, speaking as a member of the public: The draft report does not necessarily comport well with the findings on the relative risk of experiments involving evasion of immunity. Specific biosafety and biosecurity measures that have been adopted in some labs subject to the moratorium on GOF research should be highlighted.

Ryan Ritterson, Gryphon Scientific, speaking as a member of the public: Many researchers have stopped work because they were concerned that their research might be subject to the moratorium, without knowing for sure. NSABB should recommend providing points of contact who could help investigators make a determination when their research does not involve GOFROC. When biosafety risk data is collected, it should include near misses.

Corey Meyer, Gryphon Scientific, speaking as a member of the public: If ongoing monitoring of transmissibility and virulence of pathogens generated in the research will be required, this will require expertise, time, and money. NSABB should consider whether to exclude two types of research from the definition of GOFROC: research that would slightly modify a wildtype pathogen that is already highly transmissible and virulent in a way that does not change it, such as introducing a green fluorescent protein gene into the virus that causes SARS; and research that introduces genetic traits from a wildtype pathogen into a similar lab strain to understand their phenotypic consequences, making the lab strain more virulent but not exceeding the virulence of the wildtype pathogen.

Rolan Clark, comment submitted online: The federal government should create a single department to help ensure that common processes are implemented in all biological laboratories.

Nicholas Evans, University of Pennsylvania: Transparency is mentioned as a substantive value but it is not clear who the target of this transparency is, or what information should be shared with whom. It would be helpful to clarify whether the proposed external review body would review both GOFROC and DURC processes. It is not clear whether possible alternative experiments must address the same questions or only questions that are similar.

Sherry Bohn, University of Maryland, speaking as a member of the public: Biosafety officers are already overworked and need support and additional resources when there are new requirements.

Additional Discussion and Voting to Approve the NSABB Report

Key points of discussion:

- The Board discussed Dr. Meyer's comment that the definition of GOFROC potentially captures studies that are not of concern, e.g., studies that generate pathogens with pandemic potential that do not exhibit enhanced characteristics compared to the wild type (e.g. a GFP-tagged SARS virus). The Board acknowledged the comment and clarified that the intent is to capture pathogens with enhanced pandemic potential. The NSABB report provides enough information for a framework to make such decisions but specific decisions regarding individual projects are best made by institutions and federal agencies when reviewing proposals. A key component of

any process will be educating researchers and institutions about GOFROC.

- Minor edits can be made during finalization of the report, but nothing that will substantively change the NSABB's recommendations.
- "Near misses" should be added to Recommendation 3.1.
- In Principle iv, lines 1331–1339, there is ambiguity about whether alternative methods would need to address the same question or similar questions. The decision was made to change line 1337 to indicate that the alternative approach must address the same questions.
- In Recommendation 2, the word "external" in "external advisory body" could be read to mean that the committee should be completely outside of the federal government. "Independent" might be preferable. A second potential problem is with the wording "such as a committee governed by the Federal Advisory Committee Act" (FACA). There may be other options besides a FACA committee, and it could be problematic to be too prescriptive about the kind of group. The board agreed to keep the "such as…" wording as is and to remove the word "external" from "external advisory body."
- The board agreed to add the phrase "or facilitating" to Dr. Fitch's proposed Recommendation 3.2 and add that recommendation to the report, with this wording:

  > The U.S. Government should consider developing or facilitating a system to collect and analyze data about institutional review entity challenges, decisions, and lessons learned, to provide feedback to the IRE community and to inform gain of function research of concern policy development over time. Examining such data would provide a better understanding of the effectiveness and consistency of policy implementation in support of local IRE decision-making.

The Board moved and seconded the motion that the report be finalized and submitted to the U.S. government. The motion carried unanimously.

Dr. Stanley thanked the members of the working group for their efforts. In conclusion, he spoke about GOF recommendations in the context of NSABB's broader recommendations on DURC over the years. This new process for carefully evaluating GOFROC before it is funded is important and consistent with the Board's thinking over the years. It is very difficult to manage DURC at the publication stage; pre-funding review begins to avoid such situations.

The next step is for NIH to finalize the report based on discussions today, incorporating changes and minor edits. Dr. Stanley will review the final report and then ask NIH to officially submit it to the NIH director, HHS secretary, and heads of all relevant federal departments and agencies. The U.S. government will consider the recommendations and begin formulating policy.

There is still a chance to comment on this finalized report by emailing nsabb@od.nih.gov. These comments will not alter the final report but will be forwarded to OSTP to inform the policymaking process.

Dr. Stanley expressed concern that the pause in funding of GOF research may have had broader negative effects on infectious disease research. He noted it has created uncertainty in the minds of many researchers, beyond those who were directly affected by the pause, and may have discouraged

some young researchers from pursuing research in this area. He encouraged the federal government to move as quickly as possible to end the moratorium and replace it with a new oversight process for GOFROC.

Dr. Stanley thanked NSABB's federal partners, everyone who contributed to deliberative process, and the NIH staff that supports the Board. NSABB is ready to assist as the process moves forward.

The meeting adjourned at 2:14 p.m.