NSABB Working Group Report: Preliminary Findings and Draft Recommendations

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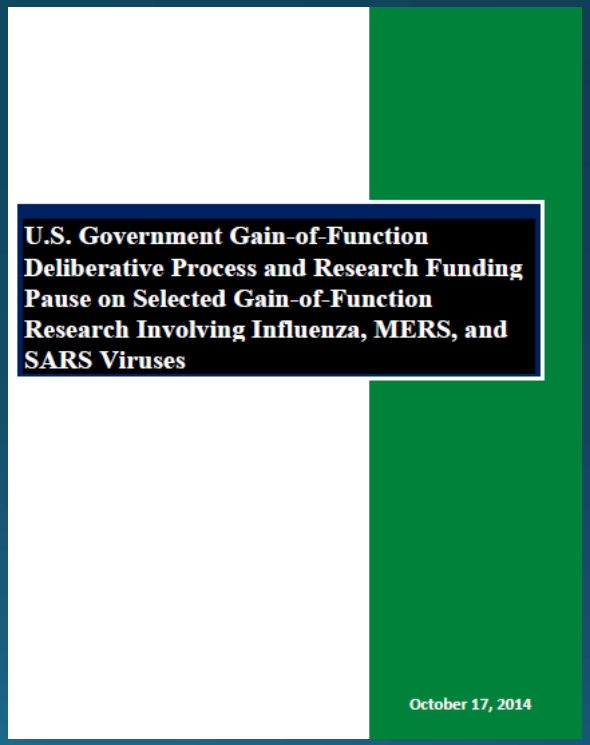
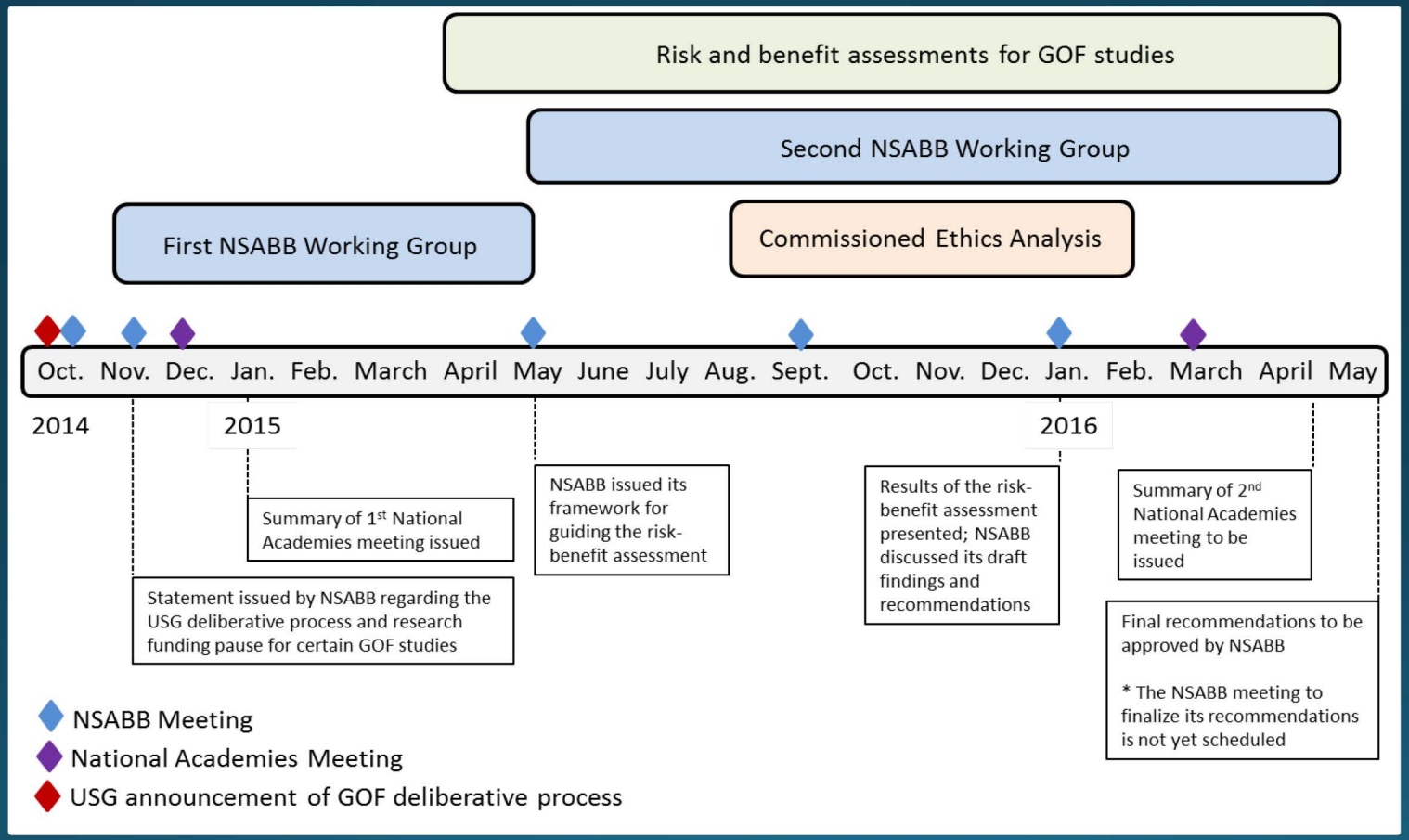
Charge to NSABB

NSABB's charge:

1. Advise on the design, development, and conduct of risk and benefit assessments for GOF studies
2. Provide recommendations to the U.S. government on a conceptual approach to the evaluation of proposed GOF studies



Timeline and Major Events of the GOF Deliberative Process

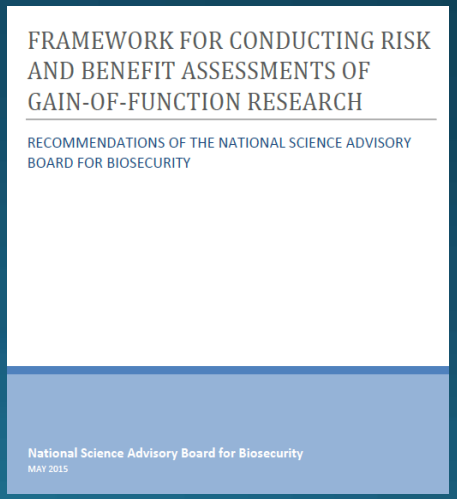


Task 1: Advising on the Risk and Benefit Assessments of GOF Studies

NSABB WG on the Design and Conduct of Risk and Benefit Assessments (RBA) of GOF Studies (Nov. 2014 – May 2015)

NSABB approved its Framework to guide the RBA in May 2015. The Framework recommended a number of features and principles to guide the development and conduct of the RBA:

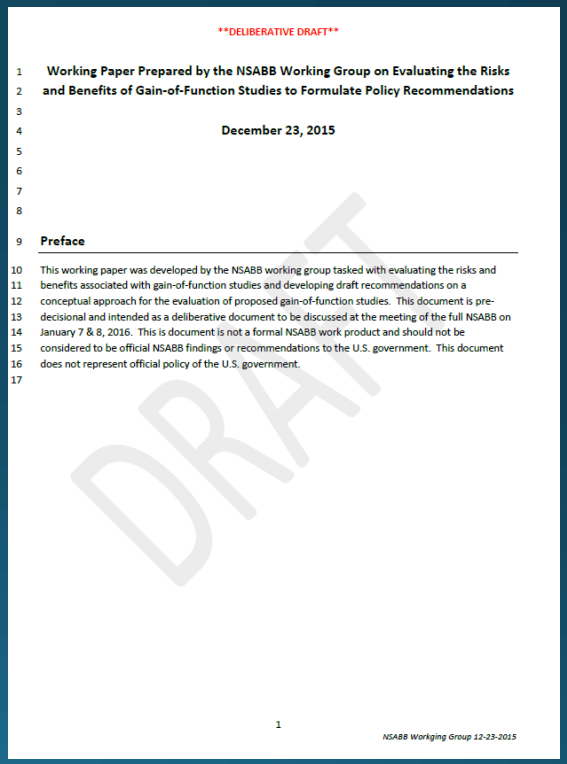
1. **Pathogens that should be included in the RBA**
2. **Pathogen characteristics that should be analyzed**
3. **Categories of risks and benefits that should be assessed**
4. **Types of scenarios and events that should be evaluated in the RA (e.g., experiment types, biosafety practices, containment features)**
5. **Methodologies for evaluating risks and benefits**



Task 2: Developing Recommendations on a Conceptual Approach to the Evaluation of Proposed GOF Studies

Working Paper on GOF studies

- Guiding principles for NSABB deliberations
- Analysis and interpretation of the RBA
- Consideration of ethical values and decision-making frameworks
- Analysis of the current policy landscape and potential policy options
- Preliminary findings from the WG's analyses
- Draft recommendations for the Board's consideration
- Important questions for further consideration



DELIBERATIVE DRAFT

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

December 23, 2015

Preface

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

DRAFT

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NSABB Workging Group 12-23-2015

Working Group Approach

1. Evaluation of potential risks and benefits of certain GOF studies

   Commissioned RBA of GOF studies (Gryphon Scientific)

2. Ethical issues and decision strategies

   Commissioned Ethical Analysis (Prof. Michael Selgelid)

3. Domestic and international policies and guidelines and potential policy options

   Briefings from subject matter experts

4. Stakeholder perspectives and broad input

   Four NSABB meetings

   1st National Academies meeting on GOF studies

   Briefings from subject matter experts

   Examination of relevant literature, readings

   Public comments

Overview of Gryphon's Risk and Benefit Assessments

Biosafety risk assessment – analysis of the risks associated with potential laboratory accidents involving GOF studies and pathogens with different enhanced phenotypes

Biosecurity risk assessment – analysis of malevolent threats as they might pertain to laboratories involving GOF research or pathogens with enhanced phenotypes

- Information risk assessment – examines the risks resulting from the misuse of information that might be generated by certain GOF studies

Benefits assessment – examines the potential benefits of GOF studies, including potential unique benefits as well as alternative approaches that may achieve the same or similar benefits

Risk and Benefit Assessments – NSABB Analysis and Interpretation

Strengths of the RBA

- Thorough, extensive, and generally in line with the recommendations in the NSABB Framework
- Analyzes a broad range of GOF studies, which facilitates identification of characteristics of the most concerning GOF studies
- Biosafety risk assessment uses a powerful parametric approach to effectively describe the relative risks associated with potential laboratory accidents involving GOF manipulations as compared to research with wild-type pathogens
- Biosecurity risk assessment is extensive and examines likely capabilities and motivations of various possible actors, and evaluates the systems in place to prevent biosecurity breaches
- Benefit assessment is thorough and identifies unique GOF benefits and alternative approaches that yield the same or similar benefits, when relevant

Risk and Benefit Assessments – NSABB Analysis and Interpretation

Limitations of the RBA

- The RBA is based on data whenever possible, but limitations in the availability and quality of that data required assumptions and estimations to be made
  - There are uncertainties associated with the input parameters that are the basis for the biosafety risk calculations (e.g., pathogen properties, frequencies of laboratory accidents)
  - Therefore, the biosafety risk assessment provides relative, not absolute estimates, of risks associated with laboratory accidents involving GOF studies
- In most cases the wild-type comparator for pandemic influenza was the 1918 strain; this may obscure significant risks associated with GOF studies that would be more apparent if the wild-type strain was a less virulent pandemic strain
- Risks and benefits are not presented in comparable terms, making it a challenge to compare risks and benefits

Key Points of the RBA

Biosafety Risks

Only some potential GOF phenotypes represent substantially increased biosafety risks

- Coronaviruses: GOF studies that would create strains with increased transmissibility among mammals may entail significant risks if they also increase human transmission
- Seasonal influenza: GOF-generated phenotypes entailing the greatest risks include enhanced transmission in mammals, enhanced virulence, and evasion of immunity
- Pandemic influenza: GOF-generated phenotypes were not predicted to greatly increase risk, however this is based on using 1918 influenza as the comparator

A variety of GOF studies were not predicted to entail significant potential risks.

Key Points of the RBA

Biosecurity Risks

- Most probable threats involve insiders who have direct access to dangerous pathogens or outsiders who collaborate with, or subvert insiders
- Information risk from future GOF studies with influenza was generally found to be small because most of the information of interest is already published, or non-GOF information relating to pathogens that are more attractive agents of harm is readily available
- There is some remaining information risk potential for certain coronavirus studies that would involve enhancing pathogenicity or transmissibility

Benefits

- Most GOF studies provide benefits in the form of new scientific knowledge; many of these benefits are unique. Examples include:
  - Coronaviruses: GOF experiments that enhance mammalian pathogenicity for developing animal models for studying disease and developing countermeasures provide unique benefits
  - Seasonal influenza: GOF experiments that increase growth of seasonal influenza vaccine candidates in culture provide unique benefits to current production of seasonal flu vaccines
- Other GOF studies were found to be valuable for surveillance and preparedness efforts, although other scientific advances are needed to fully realize the benefits

Consideration of Ethical Values

The following values are important to consider when evaluating research proposals involving GOF studies that might entail GOF studies or establishing mechanisms to review and/or make funding decisions:

Substantive Values

- Non-maleficence
- Beneficence
- Social justice
- Respect for persons
- Scientific Freedom
- Responsible Stewardship

Procedural Values

- Public participation & democratic deliberation
- Accountability
- Transparency

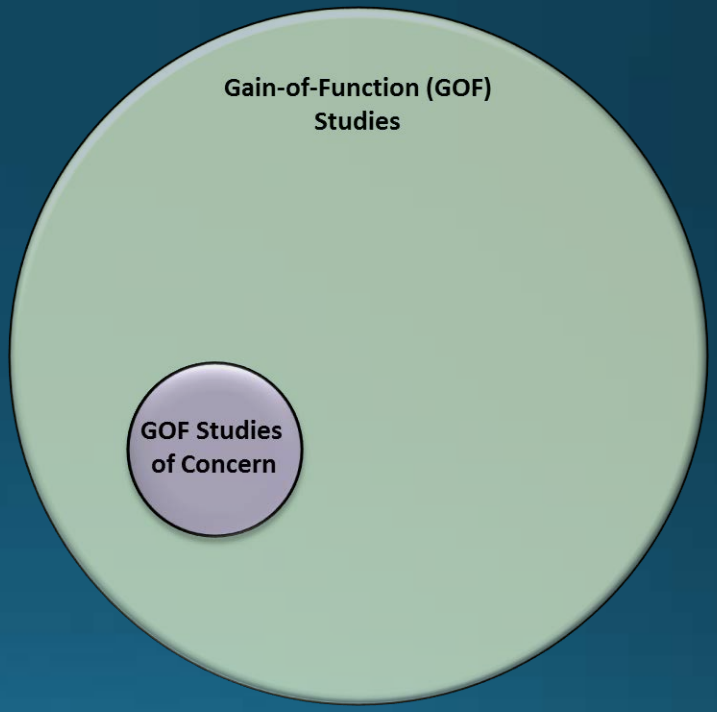
Overview of the Current Policy Landscape

- Scientific Merit Review
- Biosafety Oversight
  - *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*
  - *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*
- Federal Select Agent Program
- Federal and Institutional Oversight of Life Science Dual Use Research of Concern
- HHS Framework for guiding funding decisions about certain GOF studies
- Sharing and Communicating Scientific Findings and Research Products

Key Findings of the NSABB WG

Finding 1. There are many types of GOF studies and not all of them have the same level of risks. Only a small subset of GOF studies—GOF studies of concern—entail risks that are potentially significant enough to warrant additional oversight

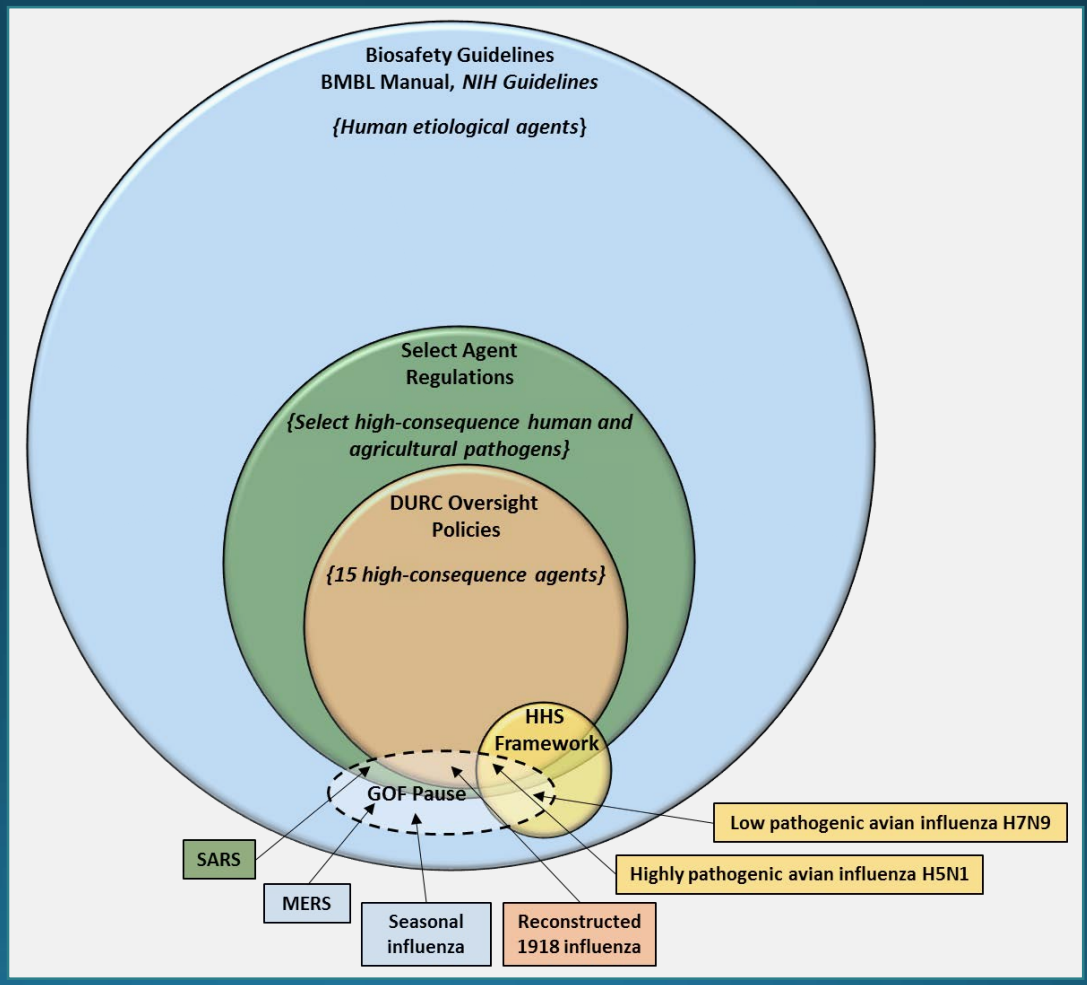
GOF studies of concern are those that could generate a pathogen that is highly transmissible, highly virulent, and likely to be resistant to control measures



Key Findings of the NSABB WG

Finding 2. The U.S. government has effective policy frameworks in place for managing risks associated with life sciences research. There are several points throughout the research life cycle where, if the policies are implemented effectively, risks can be managed and oversight of GOF studies could be applied.

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



Key Findings of the NSABB WG

Finding 4. There are life sciences research studies that should not be conducted on ethical or public health grounds if the potential risks associated with the study are not justified by the potential benefits. Decisions about whether GOF studies of concern should be permitted will entail an assessment of the potential risks and anticipated benefits associated with the individual experiment in question. The scientific merit of a study is a central consideration during the review of proposed studies but other considerations and values are also important.

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

Working Group Draft Recommendations

Recommendation 1. Research proposals involving GOF studies of concern entail the greatest risks and should be reviewed carefully for biosafety and biosecurity implications, as well as potential benefits, prior to determining whether they are acceptable for funding.

If funded, such projects should be subject to ongoing oversight at the Federal and institutional levels.

Working Group Draft Recommendations: Identifying GOF Studies of Concern

A GOF study of concern is a study that could generate a pathogen with <u>all</u> of the following attributes:

1. **The pathogen generated is highly transmissible in a relevant mammalian model.**
2. **The pathogen generated is highly virulent in a relevant mammalian model.**
3. **The pathogen generated is likely resistant to control measures or more capable of being spread among human populations than currently circulating strains of the pathogen.**

GOF studies of concern should be subject to additional review prior to making a funding decision and throughout the course of the research, if funded

Working Group Draft Recommendations: Guiding Funding Decisions for GOF of Concern

The following principles should guide the review of and funding decisions about research proposals anticipated to involve GOF studies of concern

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

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

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

Working Group Draft Recommendations: Guiding Funding Decisions for GOF of Concern

Guiding principles continued

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

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

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

vii. The proposed research is ethically justifiable.

Proposed Conceptual Approach for Funding Potential GOF Studies of Concern

1. Identify proposals anticipated to involve GOF studies of concern
   Anticipated to generate pathogen with the 3 characteristics

2. Review proposal to determine whether certain criteria are met
   Apply the 7 principles

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

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

Working Group Draft Recommendations

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

Working Group Draft Recommendations

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

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

Questions for Further Consideration

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

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

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

4. How well would the working group's description of GOF studies of concern and the principles for guiding their review inform decisions about whether to fund such studies?

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

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

Comments to: nsabb@od.nih.gov

Next Steps

- National Academies meeting (March 10-11, 2016)
- Additional working group deliberations to refine recommendations in light of comments and feedback at today's meeting and the National Academies meeting
- In the spring, the NSABB working group expects to present an updated draft report, including recommendations for further discussion and potentially for finalization by the full Board
- USG will consider the Board's recommendations as it formulates policy on the GOF issue