Update from the NSABB Working Group: Proposed Framework for the Conduct of Risk and Benefit Assessments of Gain-of-Function Research

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The Charge to the NSABB

The USG charged the NSABB with two key tasks:

1. Advice on the design, development, and conduct of risk and benefit assessments of GOF studies
   - **Deliverable 1** – Framework for the design and conduct of risk and benefit assessments of GOF studies

2. Formal recommendations to the USG on the conceptual approach to the evaluation of proposed GOF studies
   - **Deliverable 2** – Recommendations to the USG informed by the results of the risk and benefit assessment studies, and additional input and information from a number of relevant sources and disciplines.

NSABB WG Roster

NSABB Voting Members

- Kenneth I. Berns (Co-chair)
- Joseph Kanabrocki (Co-chair)
- Andrew Endy
- J. Patrick Fitch
- Christine M. Grant
- Marie-Louise Hammarskjöld
- Margie D. Lee
- Joseph E. McDade
- Jeffery F. Miller
- Rebecca T. Parkin
- Jean L. Patterson
- I. Gary Resnick
- Susan M. Wolf

Federal Agency Reps.

- Dennis M. Dixon (NIH)
- Gerald Epstein (DHS)
- Meg Flanagan (DOS)
- Wendy Hall (DHS)
- Teresa Hauguel (NIH)
- Wesley Johnson (DOC)
- Betty Lee (DOC)
- Kimberly Orr (DOC)
- Christopher Park (DOS)
- Diane Post (NIH)
- David B. Resnik (NIH)

Addressing Deliverable 1: Formation of the NSABB WG

The NSABB Working Group (WG) leveraged broad expertise across diverse areas including:

- Microbiology/Immunology
- Virology
- Molecular Biology
- Genetics & Genomics
- Public Health
- Emerging Infectious Diseases
- Pandemic Preparedness
- Agriculture/Veterinary Medicine
- Vaccine & Therapeutic Development
- Biosafety
- Biosecurity
- Biodefense
- National Security
- International Policy
- Law
- Public Policy
- Ethics
- Environmental/Occupational Health & Safety

NSABB Working Group

WG Task:
To provide advice on the design, development, and conduct of risk and benefit assessments (RA/BA) of GOF studies

Approach:

- Outline the overarching principles that should underpin the risk and benefit assessments
- Identify important elements and considerations central to the RA/BA
- Consider feedback received from various stakeholders for incorporation into the RA/BA where appropriate
- Consider readings, background material, and presentations from subject-matter experts

Overview of Proposed Framework for RA/BA of GOF Research

- **Guiding principles** that should underpin the RA/BA
- **Pathogens** that should be included in the RA/BA
- **Characteristics of pathogens** with pandemic potential that are of primary concern
- **Categories of risks and benefits** that should be assessed
- Types of **scenarios and events** that should be evaluated in the RA
  - **Types of experiments**
  - **Biosafety practices** and containment features
- **Methodologies** for evaluating risk and benefit

Proposed RA/BA Framework: Guiding Principles

The WG identified the following 12 Guiding Principles that should underpin the RA/BA:

1. There are potential risks and benefits associated with certain GOF research that should be **formally and rigorously identified and analyzed**
2. Relative risks and benefits of **alternative approaches** to GOF studies should be identified and analyzed
3. RA/BA should be conceptualized so as to provide information that is useful and informative for **guiding NSABB recommendations.**
4. The scope of the RA/BA must be **sufficiently comprehensive but also appropriately focused** on the subset of GOF studies where the risk is especially significant
5. RA/BA should be thoroughly documented and strive for **clarity, transparency, consistency, and reasonableness.**
6. RA/BA should be **objective, scientifically rigorous** and utilize peer-accepted methods, including **quantitative and qualitative approaches**

Proposed RA/BA Framework: Guiding Principles (continued)

7. RA/BA should consider the impact of **risk mitigation practices, public health interventions, countermeasure effectiveness**, as well as human error
8. RA/BA should rely on data wherever possible and acknowledge **data sources, limitations, and assumptions**, paying particular attention to issues of **uncertainty and sensitivity** in the presentation of results
9. Examination of positive and negative outcomes that may result from conducting GOF research should include consideration of **probability of occurrence, magnitude of effects, and realistic timeframes**
10. The RA/BA should focus on GOF studies conducted in the US, or supported by US funding and conducted outside the US, but also account for the fact that laboratories **not funded by the US may conduct similar studies**
11. Efforts should be made to **express risks & benefits in the same terms when possible**, while noting benefits should not be limited to a reduction of risks
12. The RA should include scenarios to analyze a **range of risks** and include intentional and accidental events

Proposed RA/BA Framework: Pathogens

Pathogens recommended for inclusion in the RA/BA:

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

2. **SARS-CoV**

3. **MERS-CoV**

Proposed RA/BA Framework: Pathogen Characteristics

Pathogen Characteristics recommended for consideration in the RA/BA:

1. Enhanced virus production as a result of changes in any step of the virus replication cycle

2. Enhanced morbidity and mortality in appropriate animal models

3. Enhanced transmission in mammals (e.g. increased host/tissue range, altered route of transmission)

4. Evasion of existing natural or induced immunity or evasion of the effects of countermeasures

Proposed RA/BA Framework: Risk Categories

The WG identified six categories of risk that should be considered in developing a RA of GOF studies due to their direct or indirect potential to adversely impact human or animal health.

1. Biosafety
2. Physical and personnel security (Biosecurity)
3. Proliferation
4. Information
5. Agricultural
6. Economic

Proposed RA/BA Framework: Benefit Categories

The WG identified five categories of benefits that should be considered in BA of GOF studies due to their direct or indirect potential to impact human or animal health.

1. Scientific knowledge
2. Biosurveillance (public health, agricultural/animal, wildlife)
3. Countermeasure development
4. Informing policy decisions
5. Economic benefits

Proposed RA/BA Framework: Historical Perspectives

To aid in the consideration of the relative risks and benefits posed by GOF studies, the WG recommends **analyses of existing historical data** on the disease burden associated with the pathogens in the assessment. This analysis should include:

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

Proposed RA/BA Framework: Scenarios and Events

The WG outlined five guiding principles for the development and selection of scenarios that will be considered for detailed analysis in the RA.

1. Scenarios and events should be scientifically, politically, and socially accurate and credible
2. To the extent possible, events and scenarios should be realistic and based on actual examples
3. The overall range of scenarios should encompass high and low risk events, high and low probability events, and maximum reasonably foreseeable (highly unlikely, but still credible) events
4. The scenarios should involve events that are of concern to stakeholders, including the public, and include types that involve experimental manipulations that ultimately may be determined to be prohibited under any circumstances

Proposed RA/BA Framework: Scenarios and Events (continued)

5. Scenarios involving security threats should be plausible but not necessarily based on specific, real-life examples, and consider prior actions or expressed intent, current and reasonably achievable technical capabilities, and how readily security threats could be achieved or enabled by a certain type of GOF study.

The WG also identified fourteen categories of events to be considered in the development of scenarios. These types of events include:

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

Proposed RA/BA Framework: Types of Experiments

The WG identified six types of experiments for consideration in the RA. These experiments may be reasonably expected to result in the generation of pathogens with enhanced pathogenicity and/or transmissibility in mammals.

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

Proposed RA/BA Framework: Biosafety Assumptions

The WG recommends that existing biosafety guidance and biocontainment capabilities, both in the US and in other parts of the world, be investigated and considered.

For each agent analyzed in the RA:

- Multiple biosafety levels (BSL) be assessed so the effects of different levels of mitigation can be determined
- Effects of adequate or inadequate occupational medicine/medical surveillance programs, training, standard operating procedures, and administrative controls be examined

Proposed RA/BA Framework: Approaches and Methods

The WG recommends that the following approaches be explored and employed by the contractor, as appropriate and reasonable, to assess the risks and benefits associated with relevant GOF studies:

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

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

3. Interviews and consultations with a broad range of relevant experts about risks and benefits associated with GOF studies

Proposed RA/BA Framework: Approaches and Methods (continued)

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

5. Quantitative approaches to modeling the risks and benefits, particularly to public health (e.g., morbidity and mortality can be modeled for various scenarios)

6. Quantitative approaches to modeling economic benefits and risks

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

Proposed RA/BA Framework: Summary

- **Guiding principles** that should underpin the RA/BA
- **Pathogens** that should be included in the RA/BA
- **Characteristics of pathogens** with pandemic potential that are of primary concern
- **Categories of risks and benefits** that should be assessed
- Types of **scenarios and events** that should be evaluated in the RA
  - **Types of experiments**
  - **Biosafety practices** and containment features
- **Methodologies** for evaluating risk and benefit

Focused Discussion on the Proposed Framework for the Conduct of Risk and Benefit Assessments of Gain-of-Function Research

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Focused Discussion: Pathogens

Pathogens currently recommended for inclusion in the RA/BA:

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

NSABB Discussion:

- Do the pathogens listed adequately represent the range of concerns?
- Will the analysis adequately inform NSABB discussions on the range potential risks and benefits of GOF studies?

Focused Discussion: Pathogen Characteristics

Pathogen Characteristics currently recommended for inclusion:

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

NSABB Discussion:

- Do the pathogen characteristics listed encompass those of primary concern?

Focused Discussion: Risk Categories

Risk Categories currently recommended for inclusion in the RA:

1. **Biosafety**: laboratory accidents and/or improper storage or handling of pathogens resulting in possible exposure to laboratory personnel, accidental spread of infectious agents beyond the confines of the designated laboratory research space, transmissions leading to secondary infections, etc.
2. **Physical and personnel security (Biosecurity)**: deliberate breach of physical security and/or containment of pathogens or data as a result of malevolent acts including theft, terrorism, or intentional release. Biosecurity has both physical and personnel dimensions and encompasses external and internal threats.
3. **Proliferation**: the spread of GOF research (protocols, practices, etc.) to more laboratories, both in the US and internationally. This might enhance various categories of risk

Focused Discussion: Risk Categories (continued)

4. **Information risk**: risks resulting from dissemination of information generated by GOF studies that could enable others to generate pathogens for malevolent purposes
5. **Agricultural**: risks to agriculturally-relevant animals (e.g. chickens, pigs)
6. **Economic risks**: financial costs associated with release of pathogens including public health response, and disruption of critical economic sectors such as agriculture, manufacturing, service industry, etc.; and issues related to liability and accountability

NSABB Discussion:

- Are the current risk categories adequate and appropriate to inform NSABB deliberations?
- Of those listed, which would be most informative when developing NSABB recommendations?

Focused Discussion: Benefit Categories

Benefit Categories currently recommended for inclusion in the BA:

1. **Scientific knowledge**: encompasses the information that could be generated from GOF studies and the value of such information, relative to alternative methods, to furthering our understanding pathogens, disease mechanisms, etc.

2. **Biosurveillance**: benefits relevant to the processes of gathering, integrating, analyzing, interpreting, and communicating essential information related to threats posed by pathogens to human, animal or plant health. Specifically , examinations should include potential benefits to:
   a. **Public Health surveillance**: how GOF research may contribute to the improvement of public health efforts by aiding detection and monitoring of pathogens in the real world, or help to better recognize or predict outbreaks in human populations, and inform decision-making.

Focused Discussion: Benefit Categories (continued)

2. **Biosurveillance (continued)**:
   b. **Agricultural and domestic animal surveillance**: how GOF research may contribute to the improvement of agricultural health efforts by aiding detection and monitoring of pathogens in food-producing, domestic, or other animals so as to help to better recognize or predict outbreaks in such animals, and inform decision-making.
   c. **Wildlife surveillance**: how GOF research may contribute to the improvement of surveillance in wildlife by aiding detection and monitoring of pathogens, or help to better recognize or predict outbreaks in such animals, and inform decision-making.

Focused Discussion: Benefit Categories (continued)

3. **Countermeasure development** – involves whether and how, GOF research yields unique information that may aid in development of treatments and preventative measures. Particularly, the benefit assessment should examine the relative benefits of GOF research compared to alternative approaches for:
   a. **Therapeutics:** How the research is likely to aid discovery and development of new or more effective therapeutics.
   b. **Vaccines:** How the research is likely to aid development and selection of new or more effective vaccines.
   c. **Diagnostics:** How the research is likely to aid development of new or better diagnostic methods and products.

Focused Discussion: Benefit Categories (continued)

4. **Informing policy decisions** – how information gained from GOF studies might contribute to critical policy decisions such as public health or pandemic preparedness, countermeasure stockpiling, resource allocation, strain selection for vaccine development, etc.

5. **Economic benefits** – the financial benefits and/or cost savings associated with GOF studies e.g. diminished health care costs due to availability of vaccines or therapeutics

NSABB Discussion:

- Are the current risk categories adequate and appropriate to inform NSABB deliberations?
- Of those listed, which would be most useful to informing the development of NSABB recommendations?
- What is an adequate timeline for consideration of the benefits of GOF studies?

Focused Discussion: Scenarios and Events

The WG identified fourteen categories of events that should be included in the scenarios to be analyzed.

1. Accidents due to equipment failure, human error, and system malfunction
2. Events that lead to direct infection of lab worker(s)
3. Accidental direct release into the environment, with possible public exposure
4. Events that lead to secondary transmission of disease in the community, starting with an infected lab worker
5. Incidents that result from security failures, either building systems or personnel
6. Incidents stemming from inventory errors and those involved with laboratory transitions, such as laboratories relocating, PIs retiring, students graduating, etc.
7. Scenarios involving the escape of an infected animal
8. Scenarios that result in health and/or economic impacts on important animal species, particularly those important to the food supply

Focused Discussion: Scenarios and Events (continued)

9. Insider threats: an internal breach of security (e.g., disgruntled lab worker, infiltration of a lab by an individual with nefarious intent)
10. External threats: an external breach of security (e.g., crime, targeting of a lab for theft of agents or materials)
11. Production of novel pathogens, for malevolent acts or other illegitimate purposes, based on information published about the results of GOF research
12. Natural disasters (e.g., earthquake, hurricane, tornado)
13. Accidents resulting from conduct of GOF research under sub-standard biosafety/biocontainment conditions or practices, either in the U.S. or internationally
14. Scenarios based on alternative experimental approaches to GOF research

NSABB Discussion:

- Do the types of events adequately capture the range of risks associated with the conduct of GOF studies?

Focused Discussion: Biosafety Assumptions

The WG recommends that **existing biosafety guidance and biocontainment capabilities**, both in the US and in other parts of the world, be investigated and considered.

For each agent analyzed in the RA:

- Multiple biosafety levels (BSL) be assessed so the effects of different levels of mitigation can be determined
- Effects of adequate or inadequate occupational medicine/medical surveillance programs, training, standard operating procedures, and administrative controls be examined

NSABB Discussion:

- What biosafety considerations should be incorporated into the RA/BA to best inform NSABB evaluations of the potential risks and benefits of GOF studies?

NSABB Discussion on the Proposed Framework