Guidance for Assessing Biosecurity & Biosafety Risks

FOR THE PURPOSE OF REVIEWING RESEARCH PROPOSALS PRIOR TO FUNDING

NTI:bio

Acknowledgments

We are grateful to Coefficient Giving for their support of our work to reduce biosecurity and biosafety risks globally. This framework would not have been possible without their generous support.

Coefficient Giving

Contributors

This guidance was developed with input from an interdisciplinary group of leading experts engaged for this project. The following individuals contributed to drafting, reviewing, and editing this document. Inclusion does not necessarily indicate agreement with every element of the document. Institutional affiliations are provided for identification purposes only and do not necessarily indicate institutional endorsement.

EXTERNAL CONTRIBUTORS

Elizabeth (Beth) E. Cameron, PhD
Senior Advisor and Professor of the Practice
Brown Pandemic Center, Brown University School of Public Health

Anemone Franz, MD, MPH
Visiting Research Fellow
American Enterprise Institute

Andrew M. Hebbeler, PhD
Director of Biosecurity
Coalition for Epidemic Preparedness Innovations (CEPI)

Marc Lipsitch, DPhil
Professor of Epidemiology and Director Center for Communicable Disease Dynamics, Harvard T.H. Chan School of Public Health

Alex John London, PhD
K&L Gates Professor of Ethics and Computational Technologies
Carnegie Mellon University

Jassi Pannu, PhD
Assistant Professor and Senior Scholar
Center for Health Security, Johns Hopkins University

NTI | BIO TEAM

Jaime Yassif, PhD
Vice President, Global Biological Policy and Programs

Hayley Severance, MPH
Deputy Vice President, Global Biological Policy and Programs

Aparupa Sengupta, PhD
Senior Program Officer, Global Biological Policy and Programs

Helia Samani
Program Associate, Global Biological Policy and Programs

The Nuclear Threat Initiative led and facilitated the process of developing this document.

Attribution Note

This guidance framework was developed through collaboration under the International Bio Funders' Compact. Its publication does not necessarily indicate formal endorsement by each individual Compact signatory but reflects a shared commitment to improving approaches to biosafety and biosecurity within research funding.

Disclaimer and Conditions of Use

- As of the publication date, this guidance reflects current understanding of biosafety and biosecurity risks, is not exhaustive, and may be updated without notice as scientific knowledge, laboratory practices, and global risk conditions evolve.
- This framework is provided as a practical decision support tool based on current data and standard assumptions. It is not intended to replace professional judgment, specialized expertise, or constitute legal, financial, medical, or technical advice. Users are solely responsible for validating the results and any decisions made. This framework may not account for all variables or unforeseen circumstances, and its outputs should be independently verified prior to application. **Users must not rely solely on this framework for critical decisions.**
- This guidance does not cover proposals involving AI-enabled biological design, synthesis, or optimization that could lead to physical biological outputs such as engineered organisms, synthesized sequences, and novel biological systems; a separate review framework for such work is forthcoming.

Introduction

Biosafety and biosecurity are vital components of life science research. As such, funding for research with infectious agents or toxins should take into account the type of work being proposed, the safety and security of the setting for that work, and the potential for widespread population harm if the research were to be accidentally or deliberately misused. Therefore, funders should assess research for these risks, determine whether the research is appropriate to support, and provide resources for building biosafety and biosecurity into research that is ultimately funded.

In keeping with the International Bio Funders' Compact commitment to safety and security, the following guidance aims to assist funders in identifying and reviewing life science research proposals that could cause harm to humans due to the risk of accidental infection and transmission or deliberate misuse of biological agents studied or produced through the research. These risks may stem from the potential for accidents involving the biological agents, their deliberate misuse, and/or the unintentional or intentional misuse of research-generated information (i.e., information hazards).

This review should take place **after proposals have been assessed for scientific merit** and **should only be conducted for shortlisted proposals** that demonstrate significant value, thereby optimizing use of funder resources. In addition to this review, funders are responsible for setting clear expectations, incorporating compliance requirements into funding agreements, and taking reasonable steps to ensure that funded research is conducted in accordance with applicable national and local laws, regulations, and policies and where these are lacking, with WHO guidance. This includes standard occupational and laboratory safety, which is outside of the scope of this review.

The guidance consists of three steps. The first step, **Rapid Screening**, serves to screen out research with low biosecurity and biosafety risk, thereby helping funders efficiently allocate their limited resources to higher-risk proposals and minimizing delay to lower-risk research. The second step, **Detailed Assessment**, should be completed only for proposals that are identified as higher risk in the Rapid Screen. The third step, **Risk Mitigation**, serves to ensure that any identified biosecurity or biosafety risks are appropriately addressed through feasible mitigation measures.

In this guidance, the terms biosecurity, biosafety, and biological agents are used in line with internationally recognized definitions, as follows.

> ***Biosecurity:*** *Principles, policies, and practices that are designed to prevent the deliberate misuse of biology to cause harm.*
>
> ***Biosafety:*** *Principles, policies, and practices that are designed to protect against accidental exposure to biological agents or their inadvertent release.*
>
> ***Biological agent:*** *A microorganism, virus, biological toxin, particle, or otherwise infectious material, either naturally occurring or genetically modified, which may have the potential to cause infection, allergy, toxicity or otherwise create a hazard to humans, non-human animals, or plants.*

STEP 1 | Rapid Screening

Rapid Screening enables funders to focus resources on higher-risk proposals by filtering out research with low biosecurity and biosafety risk.

The screening process is outlined below.

1. Is the research entirely in *silico* (no wet lab work involved)?

1.1. **If yes:** At present, the implementation guidance for entirely in silico work is still under development. Please review the proposal using existing organizational or external guidelines to determine whether the research can proceed safely.

1.2. **If no**, go to question 2.

2. Does the proposal include any one or more of the following:

2.1. **RESEARCH INVOLVING PATHOGENS OF KNOWN EPIDEMIC OR PANDEMIC RISK:** Research on pathogens known to be capable of causing an epidemic or pandemic (a non-exhaustive list of pathogens of known pandemic risk can be found in the Appendix); or

2.2. **RESEARCH INVOLVING MODIFICATION OF A BIOLOGICAL AGENT TO ENHANCE ITS ABILITY TO CAUSE LARGE-SCALE HARM, FOR EXAMPLE BY ENHANCING A PATHOGEN'S TRANSMISSIBILITY OR PATHOGENICITY:** Manipulation of biological agents such that the product of the research is reasonably anticipated to be an agent with capacity for large-scale spread and damage to public health. Examples are listed in the appendix. This may include research that is reasonably anticipated to increase (a) virulence, (b) transmissibility, or (c) the ability to overcome medical countermeasures (MCMs) such that the resulting pathogen would have pandemic potential; or

2.3. **RESEARCH INVOLVING AGENTS WITH UNKNOWN RISK AND UNCERTAIN POTENTIAL FOR LARGE-SCALE POPULATION HARM:** Research on biological agents whose ability to transmit widely or cause severe consequences for human populations is unknown.

If the answer to questions 2.1–2.3 is no, funders do not need to proceed with the Detailed Assessment. They should apply standard biosafety, biosecurity, ethical, and other evaluations as with any other research. You can find examples of internationally recognized biosafety and biosecurity guidance in the Appendix.

If the answer to any of questions 2.1–2.3 is yes, further information is needed to determine the risk level of the research and to conduct a risk-benefit analysis to determine if and how the research should proceed. As funders may not have all the required information to answer all questions, they may need to ask the researchers to provide input at this stage. Funders may consider using the questions in Step 2 to shape their requests for proposals to facilitate Steps 1 and 2 of this assessment.

STEP 2 | Detailed Assessment

Proposals that are flagged in Step 1 and should proceed to this Detailed Assessment are those that present some risk of causing widespread damage to human populations. In such situations, funders should proceed to assess the magnitude of the risk and perform a risk-benefit analysis, as outlined below.

Note: Research with biological agents that have the potential for widespread harm in humans should proceed only if the funder and researcher/prospective grantee can meet four core requirements:

- **Demonstrate that their research would be conducted safely, securely, and responsibly;**
- **Show that measures have been taken to minimize residual risk;**
- **Provide adequate assurances of substantial public health benefits expected in the near term with a plausible plan for equitable global distribution of these benefits;**
- **Demonstrate that no alternative and safer research could reach the same public health ends.**

RISK ASSESSMENT

Funders should assess the research proposed in the grant application for potential risks based on the information they have received from the Principal Investigator (PI) and any other available information. Risks could result from accidental or deliberate release of the biological agents used or generated during the research or from deliberate misuse of the information generated. Not all such risks are equal, as each depends on the probability that large-scale harm will result from the research and the magnitude of the envisioned harm. This section describes a series of questions to which answers of "yes" will generally indicate a higher degree of risk. Working through these specific questions provides a structure to assess the probability and magnitude of harm.

Questions to which an affirmative answer indicate a greater **magnitude** of potential harm:

- Does the risk involve laboratory handling of a pathogen that, under current conditions (e.g., low population immunity), could result in extensive spread beyond the current infection burden? A non-exhaustive list of pathogens of known pandemic risk can be found in the Appendix, along with toxins that could cause widespread harm to human populations through accident or deliberate misuse.

STEP 2 | Detailed Assessment

- **Can the research be reasonably anticipated to:**
  - + Increase the ability of a pathogen to transmit within a species or between species;
  - + Increase ability of the biological agent to cause disease or severity of disease caused (this also covers toxins);
  - + Increase the toxicity of a known toxin or produce a novel toxin;
  - + Increase a biological agent's stability or ability to disseminate;
  - + Increase the ability of a biological agent to interact with specific cell types or host species (altering host range or tropism);
  - + Reduce the ability of a biological agent to be detected by laboratory or surveillance method (evade detection methods and diagnostics);
  - + Increase resistance of a pathogen, toxin, or biological agent to clinical and/or veterinary prophylactic or therapeutic treatments or prevention measures, including vaccines;
  - + Enhance the susceptibility of a host population to a pathogen or toxin;
  - + Generate, reconstitute, or re-create an eradicated or extinct biological agent or toxin;
  - + Increase the potential for a biological agent to be used as a severely harmful biological material or as a biological weapon.

- **If the proposal involves research on a pathogen with unknown characteristics, could it potentially spread widely among humans?**
  - + The following questions can help determine whether an unknown pathogen has the potential to spread widely in humans:
    - Are the hosts from whom the virus was sampled species that have been the source of spillover events that have led to epidemics or pandemics in the past?
    - Is the virus known to be closely related to known zoonotic pathogens or to use receptors in common with known zoonoses?

- **Could scientific knowledge and methods generated to understand and manipulate the biological and epidemiological properties of pathogens for use in public health be repurposed by malicious actors to intentionally cause harm?**

STEP 2 | Detailed Assessment

Questions to guide assessment of the **probability** of large-scale harm:

- What are the planned procedures for this research, and how might they increase risk?
  - + **Aerosol-generating procedures:** Are there procedures that could create infectious aerosols?
  - + **Large-scale manipulations:** Are large volumes or high concentrations of the pathogen being used?
  - + **Animal use:** Is the experiment likely to create favorable conditions for human transmission due to use of infected animals in conducting the research?
  - + **Novel techniques:** Are new or untested methods being employed that could introduce unforeseen risks?

- What is the biosafety classification of the facility in which the work will be done, and what is the meaning of this classification in the jurisdiction in which it will be performed (as biosafety classifications vary by jurisdiction)?

- What is the level of expertise, experience, and effort of the safety personnel dedicated to the project?

- What is the research institution's track record? Do they have a reputation for strong biosafety and biosecurity practices?

STEP 2 | Detailed Assessment

Risk-benefit analysis: This step should serve to assess the public health benefit of the proposed research and to consider potential alternative approaches. We assume the benefits have been thoroughly assessed prior to this risk review. The goal of this section is not to fully rearticulate the benefits, but to assess the benefits in light of biosafety and biosecurity risks.

- Can the same or similar proposed scientific information be produced by an alternative scientific approach to learning the same or sufficiently similar information with lesser risk? For example, rather than a gain-of-function to create a higher level of transmission or virulence, could loss-of-function experiments or in *silico* comparisons of existing isolates with known phenotypes provide the same or similar information?

- Can the use of comparable financial resources achieve the proposed public health benefits using an alternative scientific approach, even if that leads to different scientific information? For example, could efforts at vaccine or therapeutics development provide comparable public health benefits without increasing pandemic risk?

- From the funder's perspective, are the scientific and social benefits that are anticipated to result from the proposed research sufficiently important and likely that they outweigh the risks associated with the research compared to use of the same funds for other safer alternatives? This assessment should include an accounting for the potential inequities between those who would benefit and those who would be subject to the risks.

STEP 3 | Recommended Risk Mitigation Measures

Once Steps 1 and 2 are complete, if the funder believes the research should still proceed, then funders can use this section to guide grantees on potential risk mitigation measures necessary for research to proceed. These measures aim to prevent:

- Accidental release of pathogens or other biological agents;
- Theft or misuse of pathogens, biological agents, or related information;
- Public dissemination of research findings that could be exploited maliciously.

A. ASSESSING BIOSAFETY STANDARDS

- Confirm that the research will be conducted in facilities with biosafety measures aligned with **recognized international standards** (e.g., *WHO Laboratory Biosafety Manual, 4th edition*) and, where feasible, enhanced best practices recommended in **other widely used guidance** (e.g., U.S. CDC biosafety standards)?
  - + IF YES, proceed to the next step.
  - + IF NO, consider providing resources to strengthen biosafety capacity.

- Verify whether a qualified **Biosafety Officer (BSO)** reviewed and approved the laboratory facilities and research proposal to confirm they meet biosafety and biosecurity standards.
  - + IF YES, request a summary of implemented risk mitigation measures.
  - + IF NO, use the biosafety resources in the Appendix to guide the review process.

- Identify whether the institution has dedicated financing and staffing for biosafety, and/or whether the proposal includes a request for biosafety-related resources necessary to conduct the work safely.
  - + IF YES, review the adequacy of the proposed resources and plans to ensure they are sufficient to mitigate the level of risk involved.
  - + IF NO, consider providing guidance or support to strengthen biosafety capacity before funding approval, OR consider declining the proposal.

STEP 3 Recommended Risk Mitigation Measures

B. ASSESSING BIOSECURITY STANDARDS

- Determine if the grantee has a **biosecurity plan**.
  - + IF YES, review it for completeness using the categories below.
  - + IF NO, provide the grantee with guidance on key biosecurity measures (see categories below) and assess which mitigation strategies are feasible given their resources. Where gaps remain, evaluate whether the research can be conducted safely and securely using alternative methods/practices; if critical risks cannot be mitigated, the work should not proceed.

- Determine if the grantee has a **pre-publication** plan to manage sensitive research information and prevent potential biosecurity risks.
  - + IF YES, review the plan to ensure it identifies sensitive data, outlines approval processes, and includes mitigation measures for information hazards *(meaning a risk that arises when the dissemination of information—such as data, research findings, or methods—poses a high risk of being exploited by malicious actors to cause harm.)*
  - + IF NO, work with the grantee to develop a pre-publication review plan.

- Identify whether the institution has dedicated financing and staffing for biosecurity, and/or whether the proposal includes a request for biosecurity-related resources necessary to conduct the work safely *(see Table 1, Biosecurity Priority Areas and Guidance).*
  - + IF YES, review the adequacy of the proposed resources and plans to ensure they are sufficient to mitigate the level of risk involved.
  - + IF NO, consider providing guidance or support to strengthen biosecurity capacity before funding approval, OR consider declining the proposal.

C. UNEXPECTED HIGH-CONSEQUENCE FINDINGS

- Determine if the researcher has a plan to pause work and notify funders if unexpected, high-consequence findings arise. This includes, but is not limited to, findings that may pose new biosafety or biosecurity risks, have dual-use implications, or could impact public health or national security.
  - + IF YES, review the plan to ensure it includes clear reporting procedures and risk mitigation steps.
  - + IF NO, require the researcher to develop a plan before proceeding, outlining how they will pause research and notify funders of any unexpected high-consequence outcomes.

STEP 3 Recommended Risk Mitigation Measures

TABLE 1: BIOSECURITY PRIORITY AREAS AND GUIDANCE

Priority Area	Key Questions	Best Practices
Biosecurity Awareness	Are employees aware of high-risk pathogen hazards?	E-learning, intranet campaigns, annual performance reviews, scorecards for engagement
Personnel Reliability	Are personnel trustworthy and appropriately screened?	References, background checks, counselling, or integrity programs
Transport and Export Control	Are transport/export processes secure and compliant?	Certified carriers, proper documentation, export license verification
Information Security	Are sensitive data and dual-use research safeguarded?	Access control, system backups, continuity plans, staff training, publication plan that takes information hazards into account
Accountability for Materials	Are high-risk materials tracked and access-controlled?	Inventory systems, access restrictions, incident reporting protocols
Controlling Access to Goods and Services	Are sensitive biological materials (oligonucleotides), equipment, or services restricted to authorized vendors/personnel?	Supplier screening, vendor vetting, approval process for purchase, order DNA from providers who conduct sequence and customer screening
Emergency Response	Are internal and external emergency protocols in place?	Periodic drills, structured reporting, coordination with external responders
Management	Are biosecurity roles, rules, and procedures documented?	Comprehensive program, clear responsibilities, designated biosecurity managers
Physical Security	Are multiple layers of facility security implemented?	Layered barriers, access authentication, monitoring systems with cameras and alarms

Note: Refer to the Dutch National Institute for Public Health and the Environment's website and the WHO biosecurity guidance, UK screening guidance on synthetic nucleic acids for further information.

STEP 3 Recommended Risk Mitigation Measures

Research involving large-scale risks to populations may carry ethical implications that extend beyond the funder and the research team. In addition to meeting the four core requirements outlined above (at the beginning of Step 2), it may be appropriate to consult relevant stakeholders before deciding whether to support such work. Depending on the nature of the research, this could include:

- Internal compliance and oversight bodies, such as institutional safety officers, Institutional Biosafety Committees (IBCs), facility management, and other institutional bodies involved in risk management.
- External or community stakeholders who may be directly or indirectly affected, such as residents near a proposed field site, public health authorities, or community advisory boards.

Appendix: Key Resources

GLOBAL GOVERNANCE AND RESPONSIBLE USE

- Global Guidance Framework for the Responsible Use of Life Sciences: Mitigating Biorisks and Governing Dual Use Research (World Health Organization, 2022).
- Marc Lipsitch and Thomas V. Inglesby, Moratorium on Research Intended to Create Novel Potential Pandemic Pathogens, mBio 5, no. 6 (2014).

BIOSAFETY AND BIOSECURITY GUIDANCE

- Laboratory Biosafety Manual, 4th Edition (World Health Organization, 2020).
- ISO: Biorisk Management for Laboratories and Related Organisations.
- Advisory Committee on Dangerous Pathogens (ACDP), Management and Operation of Microbiological Containment Laboratories (Health and Safety Executive, 2019).
- Laboratory Biosafety and Biosecurity Risk Assessment Guidance (Sandia National Laboratories and the International Federation of Biosafety Associations).
- Biosafety in Microbiological and Biomedical Laboratories (BMBL), 6th Edition (U.S. Centers for Disease Control and Prevention, 2020).
- Canadian Biosafety-Biosecurity Standard, Third Edition (Govt. of Canada).
- Laboratory Biosecurity Guidance (World Health Organization, 2024).

RISK ASSESSMENT AND SELF-ASSESSMENT TOOLS

- Risk Assessment Tool (RAST) for Biosafety and Biosecurity (World Health Organization, 2024)
- RIVM Dual-Use Quickscan Tool (National Institute for Public Health and the Environment, The Netherlands)

PATHOGENS OF KNOWN PANDEMIC RISK

- United States Government Policy for Oversight of Dual Use Research of Concern (2024)
- Updated WHO List of Emerging Pathogens for a Future Pandemic: Implications for Public Health and Global Preparedness, *Le Infezioni in Medicina* 32, no. 4 (2024): 463–477.
- CEPI *Priority* Pathogens List

1776 EYE STREET, NW, SUITE 1000
WASHINGTON, DC 20006
(202) 296-4810
WWW.NTI.ORG

NTI.ORG

NTI_WMD

NTI_WMD

NUCLEAR THREAT INITIATIVE