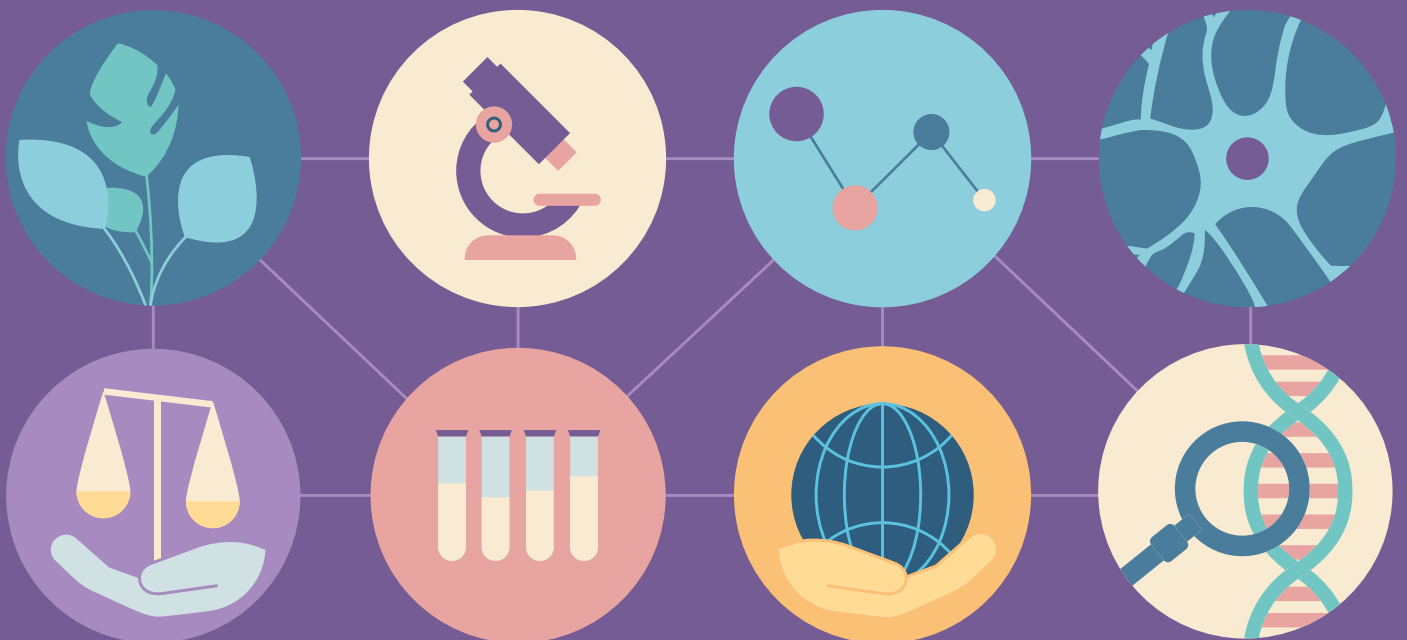


Global guidance framework for the responsible use of the life sciences

Mitigating biorisks and governing
dual-use research





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Foreword



Life sciences and technologies can offer endless opportunities to improve our health, our societies and our environment. However, developments and advances in life sciences and associated technologies may pose risks that include safety and security risks caused by accidents, inadvertent and deliberate misuse to cause harm. For example, advances in synthetic biology can have beneficial applications in medicine, energy, and environmental remediation but can also raise safety and security concerns by enhancing the pathogenic characteristics of ordinary organisms, creating new pathogens from synthetic DNA or reconstructing extinct pathogens. Development in neurosciences can help preventing and treating neurological disorders such as Parkinson's disease and Alzheimer's disease, but new knowledge and applications can also create new risks, including those of manipulating the way we think, move or behave. These risks arising from developments in the life sciences and converging technologies need to be recognized and mitigated. This is the objective of this framework. The values, principles, tools and mechanisms described in this framework aim to support Member States and stakeholders to prevent and mitigate biorisks and govern dual-use research.

WHO plays a critical role in harnessing the power of science and innovation and provides global leadership to support Member States in translating the latest in science, evidence, innovation and digital solutions to improve health and health equity for all.

Ensuring that WHO anticipates and stays on top of the latest scientific developments and identifies opportunities to improve global health also demand frameworks and practical tools to mitigate risks, especially when developments in life science and technologies could be harmful to our people, animals, plants and environments.

This framework aims to raise awareness about the importance of biorisk management in the context of the One Health approach. It identifies some of the challenges and gaps associated with mitigating biorisks and governing dual-use research and highlights how Member States and other stakeholders can effectively start biorisk management. The framework sets out a practical step approach for implementing the framework and offers checklists for various stakeholders, scenarios and case studies on the governance of biorisks and dual-use research.

This document is intended to be a starting point for the development and strengthening of biorisk management. It provides a global perspective on the tools and mechanisms for biorisk management and will need to be adapted and contextualized to reflect Member States and stakeholders' needs and perspectives. Preventing and mitigating these risks is a shared responsibility and involves many stakeholders with different capacities. Fostering a collaborative environment across sectors, disciplines and actors at different levels (individual, institutional, national, regional and global levels) that will support and strengthen countries and stakeholders' capacities to anticipate and mitigate these risks is essential to promote trust and to proactively address challenges to global public health.

Being able to prevent and mitigate risks while bringing the best of science to health will contribute to leverage the endless opportunities that the life sciences can offer to improve our health and keeping our world safe.

Dr Soumya Swaminathan
Chief Scientist
World Health Organization

A handwritten signature in blue ink, appearing to read 'Soumya', with a long horizontal stroke extending to the right.

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Abbreviations and acronyms

AI	Artificial Intelligence
ASEAN	Association of Southeast Asian Nations
ANSM	National Agency for the Safety of Drugs and Health Products (France)
BEP	Biosecurity Engagement Program
BERTA	Biosecurity Emergency Response Training Australia
BWC	Biological and Toxin Weapons Convention
CBD	Convention on Biological Diversity
CDC	Centers for Disease Control and Prevention (USA)
cDNA	Complementary DNA
CNCB	National Consultative Council for Biosecurity (France)
CNS	central nervous system
CPB	Cartagena Protocol on Biodiversity
CWC	Chemical Weapons Convention
DARPA	Defense Advanced Research Projects Agency (USA)
DFG	German Research Foundation
DIY	Do It Yourself
DMS	deep mutational scanning
DNA	Deoxyribonucleic Acid
DURC	dual-use research of concern
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FBI	US Federal Bureau of Investigation
GIBACHT	Global Partnership Initiated Biosecurity Academia for Controlling Health Threats (Germany)
GfV	German Society for Virology
GMO	genetically modified organism
HA	Haemagglutinin
HSE	Health and Safety Executive (United Kingdom)
IAP	InterAcademy Partnership
IGSC	International Gene Synthesis Consortium
ISO	International Organization for Standardization
IBSP	International Biological Security Programme
INB	International Network on Biotechnology
JEE	Joint external Evaluation

KEFs	Committees for Ethics in Security-Relevant Research (Germany)
KNAW	Royal Netherlands Academy of Arts and Science
LMIC	low- and middle-income countries
LMO	living modified organism
MDAR	materials design analysis reporting
MENA	Middle East and North Africa
NA	Neuraminidase
NASEM	National Academies of Sciences, Engineering, and Medicine
NIH	National Institutes of Health (USA)
NRC	National Research Council (USA)
NSABB	National Science Advisory Board for Biosecurity
PI	principal investigator
PPE	personal protective equipment
P3CO	Department of Health and Human Services (HHS) Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens (USA)
R&D	research and development
RCR	responsible conduct of research
REC	Research Ethics Committee
RNA	Ribonucleic Acid
SDG	Sustainable Development Goal
UN	United Nations
UNESCO	United Nations Educational, Scientific and Cultural Organization
UNICRI	United Nations Interregional Crime and Justice Research Institute
United Kingdom	United Kingdom of Great Britain and Northern Ireland
UNSCR 1540	United Nations Security Council Resolution 1540, 28 April 2004
USA	United States of America
USDA	United States Department of Agriculture
VIRS	Visibility Initiative for Responsible Science
WOAH	World Organisation for Animal Health
WHO	World Health Organization
ZKBS	Central Committee on Biological Safety (Germany)

Glossary¹

Accident

An unintended occurrence that results in harm, such as infection, illness or injury in humans, nonhuman animals, plants and agriculture, or contamination of the environment.

Awareness raising

Provision of information for the scientific community and the broader global community of the importance of biorisks as an essential part of responsible working practices in basic and applied life sciences.

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, nonhuman animals or plants.

**Biological diversity
(biodiversity)**

The variability among living organisms from all sources, including terrestrial, marine and other aquatic ecosystems, and the ecological complexes of which they are part; this includes diversity within species, between species and of ecosystems.

Biorisk

The probability or chance that an event caused by accidents, inadvertent or deliberate misuse of the life sciences can adversely affect the health of humans, nonhuman animals, plants and agriculture, and the environment.

Biorisk management

An integrated, overarching approach to address the risks associated with the life sciences research enterprise, from accidents and inadvertent actions to deliberate misuse. Biorisk management relies on three core pillars: biosafety, laboratory biosecurity and the oversight of dual-use research. Biorisk management involves the quantitative or qualitative forecasting and evaluation of the probability of harm occurring and subsequent consequences (risk assessment), together with the identification and implementation of technologies, measures or practices to avoid or minimize their likelihood or impact (risk mitigation).

¹ Some of the terms referenced in this glossary may have different meanings in other situations; however, the terms with the explanations of their meanings apply within the context of this framework.

Biosafety

Containment principles, technologies, measures and practices that are implemented to prevent unintentional exposure to biological agents or their inadvertent release.

Biosecurity

Principles, technologies, measures and practices that are implemented for the protection, control and accountability of biological agents, data or equipment, biotechnologies, skills and information related to their handling. Biosecurity aims to prevent their unauthorized access, loss, theft, misuse, diversion or release.

Civil society networks

Groups or organizations working in the interest of citizens but operating outside of the governmental and for-profit sectors.

Codes of ethics

Nonlegislated guidelines intended to establish standards of practice.

Collaborative ambition

A situation in which people collaborate to achieve a common ambition, which can mean that people put more into and get more out of activities such as work and advocacy, where those activities benefit both themselves and others.

Converging technologies

The integration of insights, principles, approaches and actors from originally distinct fields.

Disinformation

False information that is deliberately created or disseminated with the purpose of causing harm. The person disseminating disinformation knows it is false.

Dual-use

Knowledge, information, methods, products or technologies generated by peaceful and legitimate research that may be appropriated for non-peaceful or harmful purposes.

Dual-use research

Research conducted for peaceful and beneficial purposes that has the potential to produce knowledge, information, methods, products or technologies that could also be intentionally misused to endanger the health of humans, nonhuman animals, plants and agriculture, and the environment. In the context of this framework, it refers to work in the life sciences, but the principles are also applicable to other scientific fields.

Dual-use research of concern

Dual-use research of concern (DURC) describes research that is conducted for peaceful and beneficial purposes, but could easily be misapplied to do harm with no, or only minor, modification. This term has generally been used for research in the life sciences. DURC encompasses everything from information to specific products that have the potential to create negative consequences for health of humans, nonhuman animals, plants and agriculture, and the environment.

Education

The systematic provision of knowledge, competencies, skills and tools on aspects on biorisks.

Empowerment

Strengthening of the processes of engagement to increase active participation in activities such as agenda setting and priority setting.

Engagement

Efforts to involve scientists, the scientific community and other stakeholders in biorisk management and governance efforts.

Gain-of-function research

Research that results in the acquisition of new biological phenotypes, or an enhancement of existing phenotypes. Gain-of-function research that is anticipated to enhance the transmissibility or virulence (or both) of potential pandemic pathogens raises significant biosafety and biosecurity risks, as well as dual-use concerns that may warrant additional oversight.

Global health security

The multisectoral activities required, both proactive and reactive, to minimize the risk of public health events that endanger the health of humans, nonhuman animals, plants and agriculture, and the environment, across national boundaries, geographical regions and generations.

Governance

The norms, values and rules of the processes through which public affairs are managed so as to ensure transparency, participation, inclusivity and responsiveness. Governance also represents the structures and processes that are designed to ensure accountability, transparency, responsiveness, adherence to the rule of law, stability, equity and inclusiveness, empowerment, and broad-based participation.

Hazard

An object, situation or information that has the potential to cause harm to humans, nonhuman animals, plants and agriculture, or the environment. A hazard does not become a “risk” until the likelihood and consequences of that hazard causing harm are taken into account.

Incident

An occurrence that has the potential to cause, or results in, the exposure of laboratory personnel to biological agents or the release of those agents into the environment, which may or may not lead to actual harm.

Infodemic

An overabundance of information of varying quality that surges across digital and physical environments during an acute health event. An infodemic makes it harder for people to find trustworthy sources and reliable guidance when needed. When occurring during an epidemic, its potential threat for public health is significantly amplified.

Intergenerational justice

A commitment to the fair distribution of (sometimes scarce) resources across different age groups, often with a focus on future generations.

Life sciences

All sciences that deal with living organisms, including humans, nonhuman animals, plants and agriculture, and the environment, or products of living organisms or that incorporate components derived directly or synthetically from living organisms; the life sciences include but are not limited to biology, biotechnology, genomics, proteomics, bioinformatics, pharmaceutical and biomedical research and technologies.

Misinformation

Information that is false, but not intended to cause harm. Determining the veracity of information or misinformation relies on assessing the state of evidence and expert consensus on the topic. The person disseminating it may believe it to be true. It involves two dimensions: intentionality (harm/benefit – as variously defined), and knowing or not knowing that the content is false. It is not about opinion, because that cannot be fact-checked.

One Health

An integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems. It recognizes the health of humans, domestic and wild animals, plants and the wider environment (including ecosystems) are closely linked and interdependent. The approach mobilizes multiple sectors, disciplines and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems, while addressing the collective need for clean water, energy and air, safe and nutritious food, taking action on climate change and contributing to sustainable development.

Participatory governance

Governance focused on deepening democratic engagement.

Pathogen

A biological agent capable of causing disease in humans, nonhuman animals or plants.

Policies

Include laws, regulations, standards, guidelines, best practices, codes of ethics, research review processes, training and education.

Publics

Groups of the population. Just as there is no monolithic “science”, there is no unified “public”. This term is used to emphasize the plurality and diversity of perspectives, locations and engagement of groups and collectives.

Risk

A combination of the probability of harm occurring and the severity (consequences) of that harm if it were to occur.

Risk assessment

A systematic process – quantitative or qualitative – of gathering information and evaluating the nature, probability and magnitude of potential harms and determining the appropriate control measures to minimize or otherwise mitigate the risks.

Risk management

The quantitative or qualitative forecasting and evaluation of the probability of harm occurring and subsequent consequences (risk assessment) together with the identification and implementation of technologies, measures or practices to avoid or minimize their likelihood or impact (risk mitigation).

Scientific community

A network of interacting scientists, technicians and other actors (public or private) involved in research organizations, life sciences funding, standard setting, project management, publication, dissemination, development and commercialization, education, training, regulation and governance, as well as academics and scholars, including social scientists and humanists.

Scientist

A person with expertise in natural or social sciences who systematically uses research and gathers information for knowledge production.

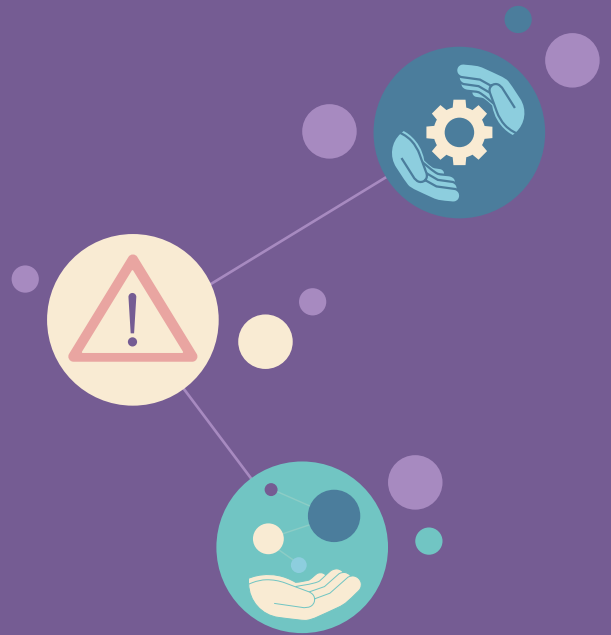
Social justice

A concern with equity and fair access to social goods such as rights, privileges and opportunities. It differs from distributive justice, which is about the fair distribution of quantifiable goods (e.g. vaccines, food and shelter). Social justice aims to ensure that political and social structures do not entrench systematic disadvantages in society.

Stakeholders

Persons or groups that have an interest in a policy or activity. They include scientists, the scientific community, ethics committee members, institutional and repository managers, biosafety officers, funding bodies, publishers, editors, security officials, regulators, institutional and other authorities, civil society networks, the private sector, other relevant organizations and publics.

Executive summary



Life sciences research and associated technologies play a critical role in improving global health, supporting healthier populations worldwide and promoting health equity for all to achieve the health-related United Nations Sustainable Development Goals (SDGs). Research and applications in the life sciences and converging technologies contribute to a better understanding of diseases, to the development of new drugs, vaccines, innovative treatment and medical devices and to the implementation of preventive measures in public health. The key objectives of the World Health Organization (WHO) for global health research are anticipating scientific, technological and epidemiological shifts; setting a global research agenda to address gaps, emerging areas and country priorities; and strengthening public confidence in science. However, developments and advances in the life sciences raise ethical, legal, societal, safety and security risks. **This document focuses on the role that responsible research can play in preventing and mitigating risks caused by accidents, unanticipated and deliberate misuse with the intention to cause harm to humans, nonhuman animals, plants and agriculture, and the environment.**



Assessing, mitigating and monitoring the safety and security risks associated with life sciences research and converging technologies is a complex endeavour. This is because the same scientific information and technologies that can generate potential benefits for health and society can also be misused to cause harm to humans, nonhuman animals, plants and agriculture, and the environment. There is also always the potential during life science research for accidents to occur that unintentionally result in harm to humans, nonhuman animals, plants and agriculture, and the environment. This raises the challenge of how to develop and implement governance tools and mechanisms that mitigate the risks posed by life sciences research, without hampering their development and use for global health and society.



The governance of biorisks is an issue that should engage all countries, although countries will have different contexts, needs and starting points. In today's interconnected world, scientific collaboration is increasing and information is rapidly disseminated. Moreover, diseases and the potential consequences of accidents, unanticipated and/or deliberate misuse can be devastating (e.g. global spread of disease). Measures for the governance of biorisks have been developed by several Member States, academia and scientific bodies, funding bodies, publishers, editors and other relevant stakeholders. However, governance and oversight frameworks to manage the risks posed by science and technologies lag behind developments and innovation in the life sciences. There are several reasons for this situation, including the rapid development and diffusion of biotechnology capabilities; the lack of biorisk governance structures in many countries and the increasing convergence of the life sciences with other scientific fields (e.g. chemistry, artificial intelligence and nanotechnology). In addition, there is a critical lack of awareness of these biorisks and a lack of incentives to identify and mitigate such risks.

Ensuring that scientific advances in the life sciences are used for the betterment of humans and the biodiversity of our planet requires collaboration among different stakeholders and disciplines. To support this collaboration and to strengthen safe, secure and responsible practices in the life sciences, the Global guidance framework for the responsible use of life sciences (hereinafter the framework) intends to provide a global perspective on the principles, tools and mechanisms to support Member States and other relevant stakeholders to mitigate and prevent biorisks and govern dual-use research.

The framework adopts an integrated approach of “biorisk management” as an overarching structure to address the full spectrum of risks associated with the life sciences research enterprise; that is, risks caused by accidents, unanticipated and deliberate misuse. Robust biorisk management relies on three core pillars: biosafety, laboratory biosecurity and the oversight of dual-use research.



This global guidance framework should be useful for audiences interesting in:

- a.** Understanding key considerations, evolving challenges and gaps in mitigating biorisks and governing dual-use research;
- b.** Having guidance on a common set of values and principles to guide decision-making and on tools and mechanisms to effectively mitigate risks posed by the life sciences, while ensuring the beneficial use of the life sciences for global health and society;
- c.** Practical step approach, pathways for governance and checklists for distinct stakeholders associated with the governance of biorisks and dual-use research;
- d.** Scenarios and case studies that illustrate the challenges and priority actions in the governance of biorisks and dual-use research.

More specific and practical toolkits that address different contexts and audiences will be developed in collaboration with regions, countries, international organizations and other relevant stakeholders to facilitate its use and operationalization at large.

The framework is divided into six sections.



Section 1 introduces key considerations and gaps in the governance of biorisks, the rationale for WHO's engagement in this topic, the aims, scope and audiences of the framework and the process leading to its development.



Section 2 highlights the evolving challenges and major gaps in the governance of biorisks.



Section 3 outlines the values and principles, and their associated commitments, that underpin the framework and should guide the development and implementation of effective biorisk management policies by Member States, and the actions of relevant stakeholders. This section also outlines key elements of good governance of biorisks.



Section 4 identifies practical tools and mechanisms for the governance of biorisks, arranged by different groups of stakeholders who have responsibilities in the oversight of biorisks. This section covers both formal and informal governance measures at individual, institutional, national, regional and international levels. It aims to reach different communities associated with the life sciences, from scientists and technicians, research institutions, funders and publishers, to those communities working with disciplines that intersect with the life sciences (e.g. chemistry, artificial intelligence and computer science).

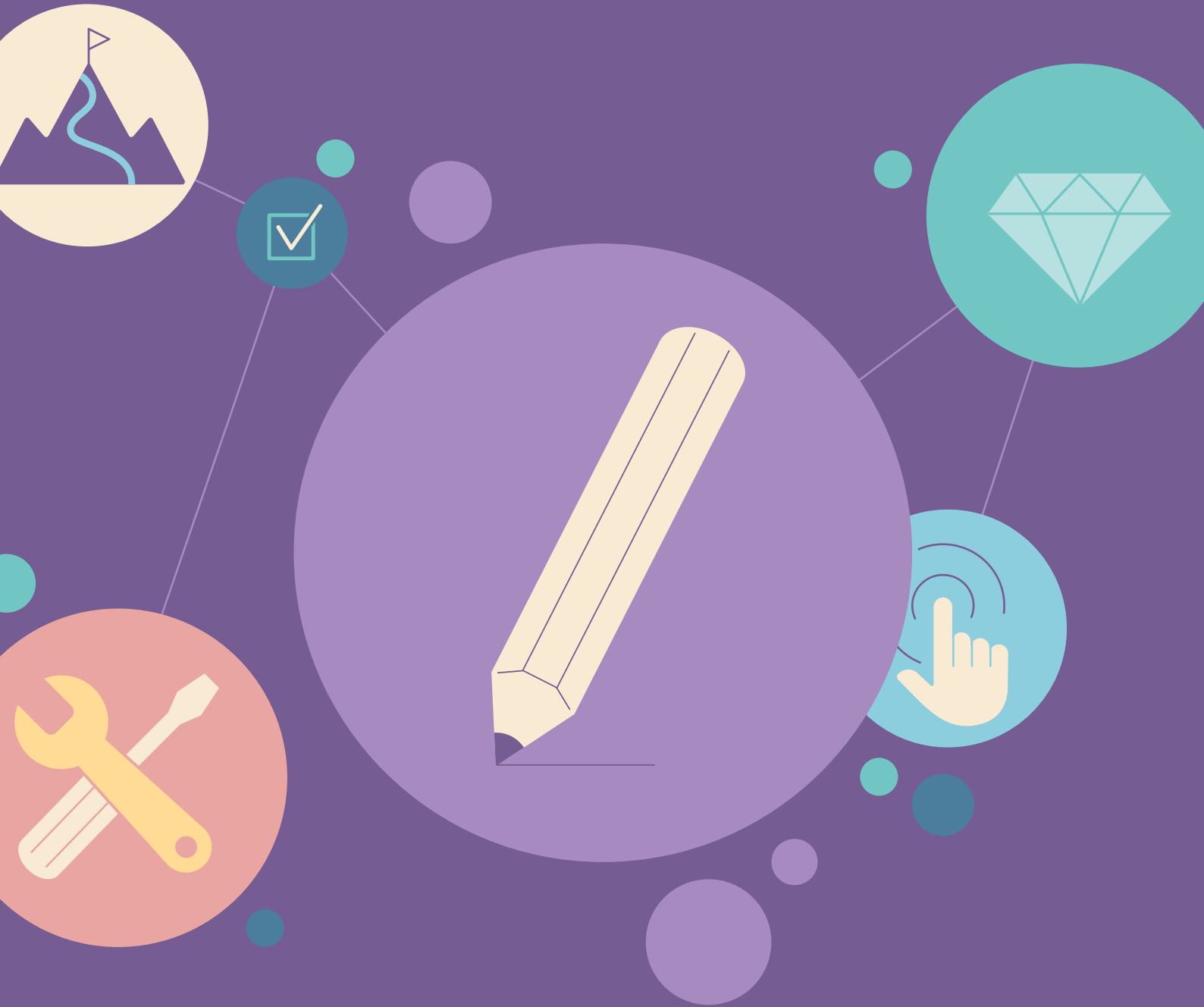


Section 5 describes a step-by-step approach with checklists applicable to different stakeholders to start implementing the framework within their own contexts and settings. It pulls together the various elements of the framework, and outlines the steps in terms of stakeholders, tools and mechanisms, principles and values, and key questions for the governance of biorisks.



Section 6 makes conclusions and highlights critical elements for the responsible use of life sciences.

In addition, there are three annexes. **Annex 1** provides seven scenarios that have been designed to further assist in the implementation of the framework. **Annex 2** puts forward three case studies that illustrate challenges and gaps in the governance of biorisks. Finally, **Annex 3** lists examples of awareness raising, education, training and capacity-building in the life sciences and related fields in different countries.



1. Section 1

Introduction

1.1 Context



Advances in life sciences research and converging technologies hold great promise for new and improved ways to address global health and support healthier populations worldwide. They contribute to the development of new diagnostics, drugs, vaccines, innovative treatment and medical devices; to the implementation of preventive public health measures; and to the promotion of food safety and security. They are critical for realizing the United Nations (UN) health-related Sustainable Development Goals (SDGs). Moreover, new scientific information and techniques are crucial for responding to public health emergencies. Life sciences research and innovation have accelerated the development of diagnostics, therapeutics and vaccines to address the coronavirus disease (COVID-19) pandemic (1). During this pandemic, an immense and unprecedented global collaboration among scientists and other experts has been taking place across all key research areas (2).



Scientific and technological advances in the life sciences and converging technologies can raise significant ethical, legal, societal, safety and security risks. This framework focuses on the safety and security risks of health-related research caused by accidents, inadvertent or deliberate misuse with the intention to cause harm. The same scientific information and technologies that can generate potential benefits for health and society could also accidentally or deliberately be misused and potentially cause harm to humans, nonhuman animals, plants and agriculture, and the environment. This raises the challenge of how to develop and implement governance tools and mechanisms that mitigate the risks posed by life sciences research, without hampering the development and use of such research for global health and society. Moreover, irrespective of whether risks arise from the latest developments in the life sciences or from well-established practices, all life sciences research and applications must be used responsibly.

Risks can arise from unintentional actions

Risks can arise from unintentional actions; for example, from accidents that occur in the course of research resulting in harm (e.g. infection, illness or injury in humans, nonhuman animals or contamination of the environment). Accidents can happen in laboratories (3) but also outside of laboratory premises; for example, through field sampling activities or incidents involving the handling, sampling, packing, transport and storage of biological substances. It is therefore important to ensure continual review and improvement of risk control measures.

Risks can stem from unanticipated findings that could potentially cause harm

Risks can stem from unanticipated findings that could potentially cause harm. Researchers may discover unexpected results during their research and experiments; for example, they accidentally increased the virulence of mousepox as part of an experiment to control mice as pests (4).

Risks can also stem from inadvertent applications of research with outcomes which are applied in harmful or potentially unethical ways unanticipated by the researcher

Risks can stem from unintended application of research with outcomes that are applied in harmful or potentially unethical ways unanticipated by the researcher. Risks can also stem from intentional application with no harm intended. For example, a genetically modified organism (GMO) containing an engineered gene drive could be released intentionally after an assessment and approval process, but its release could lead to unanticipated harms to humans, nonhuman animals, plants and agriculture, and the environment.

Risks can arise from the deliberate misuse of life sciences research, knowledge, materials and skills to cause harm

Risks can arise from the deliberate misuse of life sciences research, knowledge, materials and skills to cause harm. Existing and emerging scientific information and techniques developed for the public good could be misused to cause harm. For example, the sending of letters containing anthrax in the United States of America (USA) in 2001 is a case of deliberate misuse of a biological agent with the intention to cause harm.



Accidents, inadvertent and deliberate misuse of life sciences research and technologies can cause different types of harm. Well-intentioned research that involves the creation, transfer or use of enhanced pathogens of pandemic potential as well as gain-of-function research could pose risks to society if such pathogens were inadvertently released outside of the laboratory. Although research on infectious diseases is critical for improving our responses to diseases (e.g. through prevention, diagnosis and treatment), accidents involving pathogens or the deliberate misuse of infectious biological agents could generate infections and diseases that could harm global health and societies. For example, advances in synthetic biology, which is the application of science, technology and engineering to facilitate and accelerate the design, manufacture or modification of genetic materials in living organisms (5), can have beneficial applications in medicine, energy and environmental remediation. However, these advances can also create safety and security concerns; for example, by conferring or enhancing pathogenic characteristics to ordinary organisms, through the creation of new pathogens from synthetic DNA (6) or the reconstruction of extinct pathogens (5, 7). Artificial intelligence (AI) technologies for drug discovery could also potentially be misused to identify toxic molecules (8). But potential harms could also arise from other areas of the life sciences, not solely from pathogens and toxic molecules. Neuroscience provides a greater understanding of the functions of the brain and can help to prevent and treat neurological disorders such as Parkinson's disease and Alzheimer's disease. However, research in this field could be misused to manipulate the way we think, move or behave. Rapid advances in the life sciences and converging technologies could enable the manipulation of fundamental life processes "including the processes of cognition, development, reproduction, and inheritance" (9). Similarly, the use of big data has the potential to transform health care but concerns have been raised (e.g. about health data security, including safeguarding privacy) (10). Moreover, misinformation and disinformation about dual-use research could cause mistrust, confusion, discord and harm.



Governance of biorisks is relevant to all countries; however, levels of governance vary among countries, with some already having some elaborated systems to manage biorisks and others considering developing new systems or leveraging existing systems. The use of foresight approaches, such as horizon scans or scenario assessments, can help governance actors to proactively identify emerging technologies and issues, to respond in a timely manner to advances in science and technology, and develop appropriate governance frameworks.

Over the past 2 decades, a variety of measures, rules, regulations and codes of conduct for the governance of biorisks have been developed ([Section 2](#) and [Section 4](#)).

At the international level, the 1925 Geneva Protocol (11) bans the use of chemical and biological weapons in war and is considered international customary law. The 1972 Biological and Toxin Weapons Convention (BWC) (12), which builds on the 1925 Geneva Protocol, prohibits the development, production, stockpiling and use of biological and toxin weapons. The 1993 Chemical Weapons Convention (CWC) (13) prohibits the development, production, acquisition, stockpiling, retention, transfer and use of chemical weapons. Both conventions – the BWC and the CWC – cover the misuse of poisonous and toxic substances, including bioregulators, as weapons.² The convergence of biology and chemistry further increases the overlap between the CWC and BWC (15, 16).³ In 2004, the UN Security Council unanimously adopted the legally binding resolution 1540 (UNSCR 1540) (17), which focuses on preventing the proliferation of nuclear, chemical or biological weapons to non-State actors. Also, several international bodies and initiatives have been addressing the governance of biorisks.⁴

² The CWC covers all chemicals, regardless of their origin or method of production, that interfere with life processes to cause death, temporary incapacitation or permanent harm to humans or animals (Article II.2) as well as their precursors (Article II.3). The CWC therefore covers all toxins and bioregulators because they are chemicals "except where intended for purposes not prohibited under this Convention, as long as the types and quantities are consistent with such purposes" (Art II.1(a)). The prohibition is comprehensive. Exemptions for peaceful and protective purposes are listed in Article II.9. For further information, see Krutzsch et al. (2014) (14).

³ Most World Health Organization (WHO) Member States are States Parties to both the BWC and CWC.

⁴ For example, the Global Health Security Agenda (18) and the Global Partnership Against the Spread of Weapons and Materials of Mass Destruction (19).

1.2 Rationale for this global guidance framework

Despite these various efforts and activities, governance and oversight frameworks to manage the risks posed by science and technologies and their applications lag behind developments and innovation in the life sciences.

There are several reasons for this situation. The rapid development and diffusion of biotechnology capabilities makes it challenging for governance mechanisms to keep pace with these trends. Many countries and scientific institutions lack structures for biorisk governance; also, existing governance mechanisms are often not adequate to address current technologies, let alone future ones. Life sciences are also increasingly converging with other fields such as chemistry (e.g. biochemistry and pharmacology), AI and nanotechnology (20). Risks can emerge at these interfaces and are not necessarily covered under existing biorisk frameworks. There is also a paucity of international standards or norms for preventing and mitigating these emerging health security risks.

A chronic and fundamental challenge is a widespread lack of awareness that work in this area – which is predominantly undertaken to advance knowledge and tools to improve health, economies and societies – could be conducted or misused in ways that result in health and security risks to the public. Also, incentives to identify and mitigate such risks are lacking.

With the emergence of new technologies, the convergence of the life sciences with other disciplines and the existing gaps in governance, a global guidance framework is needed for mitigating biorisks and governing dual-use research. This framework recognizes that there is no standard and unique approach that can be used to mitigate biorisks and govern dual-use research. This document is the first global, technical and normative framework that intends to set foundations to inform the development of national frameworks and approaches, taking into account the different national contexts, resources and priorities. Specific and practical toolkits will be developed to facilitate and accompany its broader use by diverse audiences.

The World Health Organization (WHO) has been active in this area of work since the late 1960s, with resolution WHA22.58 from 1969, and the publication of the report *Health aspects of chemical and biological weapons* (21) in 1970 and its second edition in 2004 (22). More recently, WHO has published guidance on responsible life sciences research (23) and convened consultations on dual-use research (24, 25). This framework has been developed by the WHO Science Division, in collaboration with the WHO Health Emergencies Programme. WHO's key objectives for global health research are anticipating scientific, technological and epidemiological shifts; setting a global research agenda to address gaps, emerging areas and country priorities; and strengthening confidence in science (26). While recognizing that the governance of biorisks cannot be under the sole responsibility of one international body, WHO, through its leadership, aims to harness the developments of the life sciences to improve global health while anticipating and mitigating risks posed by such developments.

1.3 Aims and scope

The framework aims to provide guidance, values and principles, tools and mechanisms to mitigate and govern existing and future potential biorisks and dual-use research. It has the overall objective of upholding the power of the life sciences and innovation, and their potential positive impacts on health and societies, while guarding against the potential harms that could emerge from existing and new scientific information and technologies. The framework is not intended to be prescriptive or to provide specific standards for governance.

Biorisk management

The framework adopts “biorisk management” as an integrated, overarching approach to address the risks associated with the life sciences research enterprise, from accidents and inadvertent actions to deliberate misuse. Robust biorisk management relies on three core pillars

- biosafety, laboratory biosecurity and the oversight of dual-use research
- and requires a range of tools and mechanisms to address both existing and unknown risks.

The responsible use of the life sciences is an ethical endeavour. This document recognizes that the literature on responsible conduct of research and responsible innovation is rich and encompasses a wide range of ethical issues that are broader than activities to mitigate and prevent biorisks and dual-use research. Employment of the term “responsible use” in this guidance is motivated by the desire to highlight the importance of ethics in the governance of biorisks and the intent to reach a large audience of scientists, research communities and other stakeholders, to optimize governance of biorisks and dual-use research.

The scope of the framework focuses on the risks posed by health-related research in the life sciences.

Such research that has the potential for dual-use includes research and experiments with biological agents; however, as the life sciences evolve, research with dual-use potential extends to fields such as neurosciences, bioinformatics, genome editing and synthetic biology. Moreover, other scientific disciplines (e.g. chemistry, AI, machine and deep learning, and physical engineering) are converging with the life sciences and can affect health-related research. Hence, the framework covers the dual-use potential of pathogens, biological agents and experiments of concern but also covers other life sciences research activities with dual-use potential.

The potential harms stemming from accidents, inadvertent or deliberate misuse of life sciences research and technologies can arise throughout the research life cycle. Hence, governance measures need to be taken throughout the research process, before and during the conception of a research project; during funding applications; during the conduct of research; and during the publication, translation and application of findings (27). Risks can emerge from different settings, including the public health-related research sector (e.g. universities, research institutes and other publicly funded research), the private and commercial health-related research sector (e.g. the pharmaceutical sector, in large research and vaccine production facilities and biotechnology companies), biodefence laboratories developing medical countermeasures, do-it-yourself (DIY) research spaces, non-profit entities and manufacturing facilities, and through the collection of samples during outbreaks and fieldwork. Risks can also arise from public health and medical microbiology laboratories that process and analyse samples taken from humans or nonhuman animals. Therefore, various stakeholders need to be involved in the governance of biorisks, including scientists and their institutions, funding bodies, publishers, editors, governments, civil society, security communities, DIY laboratory communities and the private sector.

1.4 Audiences

The framework is primarily intended for those who have responsibilities in the governance of biorisks, such as policy-makers and regulators in charge of developing national policies to harness the potential benefits of the life sciences while constraining their risks. The safe, secure and responsible governance of the life sciences will require the involvement and cooperation of different government ministries, including health agencies.

The framework is also directed towards scientists and research institutions, educators, trainers, project management staff, funding bodies, publishers, editors, the private sector and all relevant stakeholders that are part of the research life cycle. It aims to support citizen groups, civil society and organizations (nongovernmental, regional and international) that will, in coordination with other relevant stakeholders, be involved in the governance of biorisks.

Given the rapidly evolving challenges, managing biorisks requires a coordinated and multidisciplinary approach that fosters cross-disciplinary policies and actions, covering humans, nonhuman animals, plants and agriculture, and the environment.

The consequences of accidents, inadvertent and deliberate misuse can lead to health events that could rapidly affect distant communities, and the COVID-19 pandemic is showing us the importance of taking a One Health approach.⁵

⁵ "One Health is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems. It recognizes [that] the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and interdependent. The approach mobilizes multiple sectors, disciplines and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems, while addressing the collective need for clean water, energy and air, safe and nutritious food, taking action on climate change, and contributing to sustainable development." (28).

The framework does not address the management of responses to disease outbreaks affecting humans, nonhuman animals and plants; however, it does recognize the importance of preventing and mitigating these risks in collaboration with the relevant actors and sectors, including with the Food and Agriculture Organization of the UN (FAO), World Organisation for Animal Health (WOAH), UN Environment Programme (UNEP) and the Convention on Biological Diversity (CBD). Collaboration across sectors, disciplines and levels is critical to address global health threats and biorisks. Stakeholders from different sectors and disciplines (public health, animal and plant health, and the environment) and based at different levels (local, national, regional and global levels) should work together to support a One Health approach and promote multisectoral responses to biorisks at the human–animal–ecosystem interface. Given that the responsibility to govern these risks will fall on various stakeholders, the framework underscores the importance of both individual and collective efforts to address these risks, from the scientific community and its institutions, to Member States, funding bodies, publishers, editors, security actors and the private sector.

1.5 Methodology



2020

2021

2022

The framework builds on pre-existing work and initiatives aimed at managing the risks of accidents, inadvertent and deliberate misuse of life sciences research and technologies. It identifies lessons learned and explores collaborative efforts. Development of the framework was informed by the insights and expertise of a broad range of multidisciplinary stakeholders; for example, in **2020**, the WHO Science Division organized three dialogues with academies, science councils, publishers, editors and research donors to better understand the perspectives of different stakeholders and to identify areas for collaboration (29-31).

Following these three dialogues, an initial consultative meeting was convened on **11 March 2021** to consult on the scope, terminology and critical elements of the framework (32). As a result of this meeting, three working groups were established to provide inputs on three themes: the values and principles that should underpin the framework and guide policies in this area; the tools and mechanisms to promote the responsible use of the life sciences and minimize risks of accidents, inadvertent and deliberate misuse; and awareness raising, education, capacity-building and engagement. On **7 September 2021**, a second consultative meeting was convened to share the findings and recommendations of the three working groups and to discuss next steps in the development of the framework (33). Two additional working groups were subsequently set up to carry out particular activities: one group to develop a glossary of terms, to link the values and principles with the recommendations of the working groups and produce a document integrating the work of the three original working groups; the other to develop scenarios to test the framework and help stakeholders to identify robust biorisk management strategies. The framework draws directly on the findings and recommendations of these five working groups and has been developed in collaboration with a broad range of stakeholders and experts from around the world.

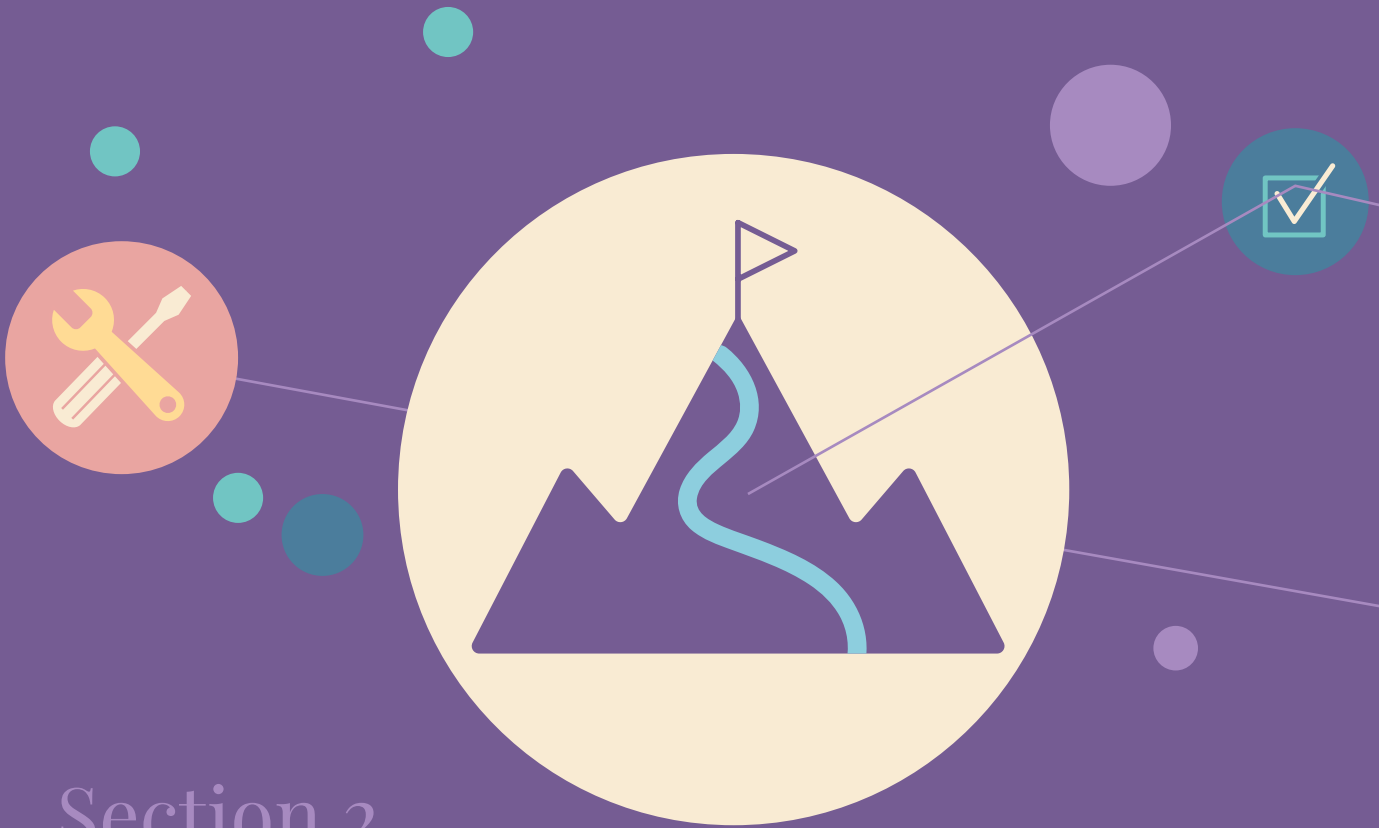
In February 2022, the draft framework was posted on the project website for public consultation over a 3-week period. Feedback received through the public consultation informed the further development of the framework. The draft framework was subsequently circulated to an external group for peer review.

The framework draws on several WHO publications that provide guidance on the governance of emerging technologies; for example, the framework for the governance of and recommendations on human genome editing (34, 35) provided critical elements in terms of approach and process; similarly, guidance on AI (10) provided relevant insights. The framework builds on the 2010 WHO publication *Responsible life sciences research for global health security* (23), and on that publication's use of biorisk management, which was based on research excellence, ethics, biosafety and laboratory biosecurity. However, whereas the 2010 guidance focused on infectious biological agents and toxins, this framework extends its scope to encompass life sciences and converging fields. The framework also draws on the fourth edition of the WHO Laboratory biosafety manual (3).

1.6 Implementation and review

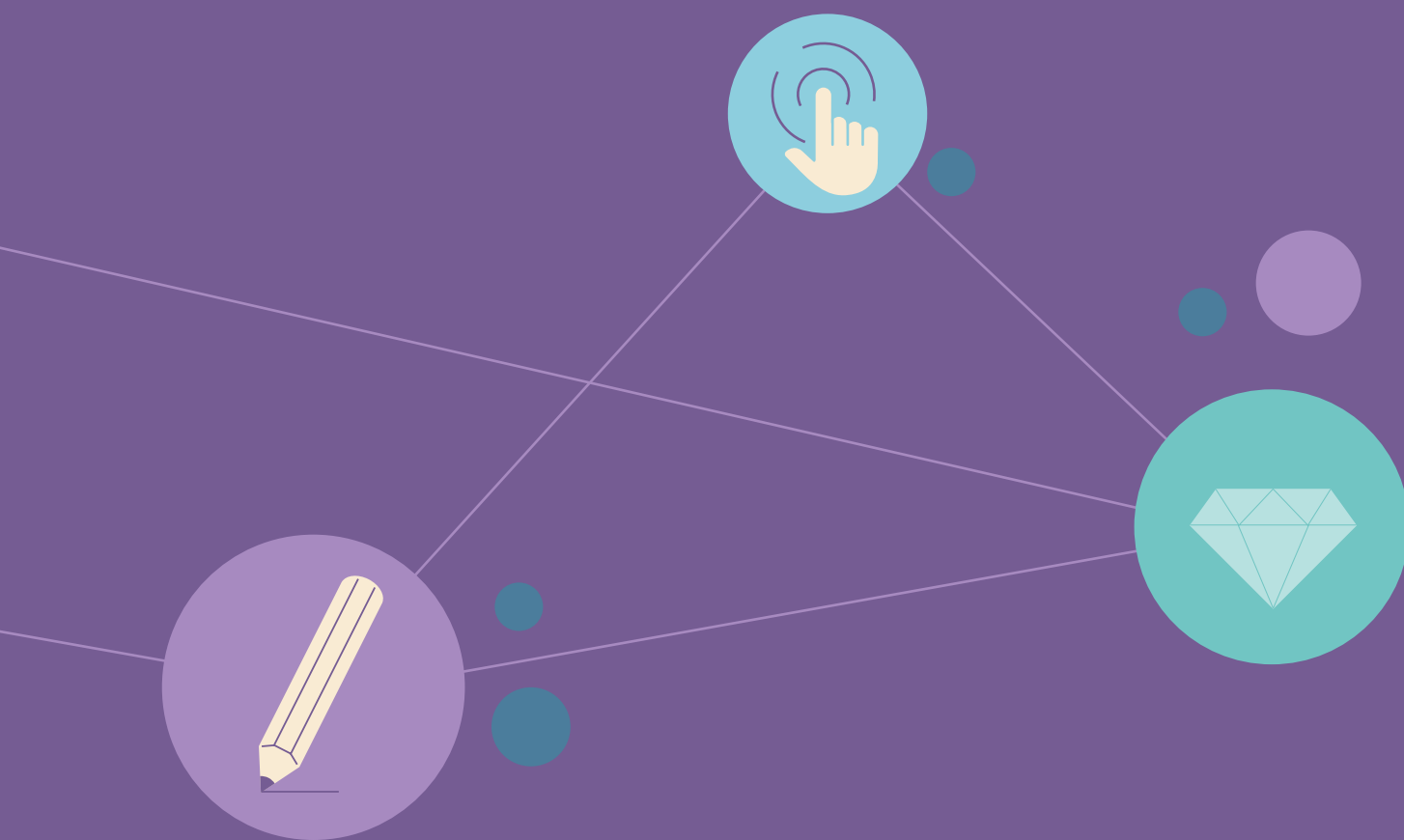
The global guidance framework is a starting point; it will need to be contextualized to the needs and priorities of different audiences. Tools for practical implementation and follow-up activities for the operationalization of the framework will be developed to facilitate implementation. Specific toolkits will be developed in collaboration with the WHO regions, Member States, international organizations and relevant stakeholders. [Section 5](#) identifies several pathways for implementation and provides checklists for different stakeholders to identify existing elements of governance and those elements that may need to be developed.

The framework is a living document. It is intended to be an iterative and proactive process that regularly re-evaluates ways in which life sciences research and technologies may create risks and ways in which elements of the framework need to keep up with societal developments. The risk landscape evolves as science and applications evolve; thus, governance strategies, including this framework, will need to be regularly reviewed and updated. The framework recognizes the importance of learning and exploring risk governance solutions; it does not provide prescriptive standards. The document will be revised based on the experience gained from its implementation by different Member States and stakeholders, and in response to technical and societal challenges, and stakeholders' needs and priorities. Some 3–5 years after publication, WHO will evaluate evidence associated with the mitigation of biorisks and the governance of dual-use research, and new developments in science and technology and their impact on governance, and on stakeholders' experiences and practices. That information will contribute to the review of this document.



2. Section 2

Evolving challenges and gaps in the governance of biorisks



Preventing the misuse of biology and other life sciences is not a new issue. There is no single solution for addressing accidents, inadvertent and deliberate misuse of the life sciences; rather, a web of preventive, complementary and synergistic measures at all levels is needed (36, 37). Likewise, governing biorisks cannot be done by a single group of stakeholders; instead, it needs to bring together multiple stakeholders with different roles and responsibilities, working together at different levels (individual, institutional, national, regional and international) and from different geographical regions. For decades, the policy-making community and relevant stakeholders have recognized and wrestled with the misuse of biology and other life sciences. There are several challenges and gaps in governance that explain this situation, as outlined below.⁶

⁶ Section 2 directly draws on the reports developed by the WHO working groups on values and principles, on tools and mechanisms for biorisk management and on awareness raising, education, training and capacity-building (not published) and on WHO (2022) (38).

2.1 Increasing pace of advances in the life sciences

Advances in the life sciences are a fast-moving and global endeavour (39). The advances are accompanied by a rapid decrease in the cost of technologies and an increase in the diffusion of knowledge and capabilities. These trends can contribute to the development of new therapeutics and vaccines, and can enhance our understanding of diseases and our ability to respond to them; however, they also have implications for the governance of biorisks.

The rapid development of the life sciences and technologies and the diffusion of biotechnology capabilities pose challenges to policy-makers, who need to keep pace with advances and innovations. Governance systems need to be flexible and responsive to scientific and technological changes – this is a systemic issue associated with the governance of emerging technologies. Many countries and scientific institutions lack biorisk governance structures, and even existing governance mechanisms are often not adequate to address current technologies, let alone future ones. The various fields of the life sciences progress at different rates, have different levels of maturity and may pose different risks. Progress is fast but not all potential advances in science and technology become a reality (16). Also, some areas of biotechnology and procedures are more subject to de-skilling (and thus to potential misuse) than others (40, 41).

Life sciences are increasingly converging with other fields such as chemistry, AI and nanotechnology (20), changing the landscape of risks. Risks that could emerge at these interfaces may not be covered by traditional biorisk frameworks, and could contribute to a diversification of risks and stakeholders. For example, synthetic biology – the application of science, technology and engineering to facilitate and accelerate the design, manufacture or modification of genetic materials in living organisms (5) – is a fast-evolving discipline of the life sciences that can have beneficial applications in medicine, energy and environmental remediation. However, concerns have been raised about the synthesis of new or existing biological agents that could potentially be deliberately misused to cause harm (5, 7).

Another issue is that new entities have entered the field of synthetic biology. Amateur communities and DIY biotechnology communities have emerged over recent years as a result of open-source access, the sharing of materials and the low cost of tools. In addition, cloud laboratories could lead to broader access to biotechnology (42), and commercial companies have entered the field of synthetic biology and DNA sequencing, contributing to a diversification of stakeholders.

New risks extend beyond pathogens and biology. For example, new developments in neurosciences could potentially be misused (e.g. to enhance or diminish human performance) (43, 44). Advances in nanotechnology and its applications in the life sciences have led to the development of nanocarriers that can improve the efficacy of drugs, but there are concerns that nanoparticles could be misused (e.g. being delivered as aerosols that could traverse the blood–brain barrier) (16). In addition, risks extend beyond human diseases to include potential harms to plants, animals and the environment. For example, research information could be deliberately misused to modify genetic information and alter the environment by introducing non-native species. Risks to public health can also stem from technologies and related information sciences. Technologies, digital and information environment are increasingly being used by health authorities for responding to health emergencies, running the health care system or implementing health programmes and policies. Yet these technologies and related information sciences can also cause some risks. There is a need to consider the dual-use potential of technology such as AI and its role in cyberwarfare including information warfare (i.e. the automated production and propagation of content, including fake video and text content). The scope of governance needs to be broadened to areas where life sciences intersect and overlap with other scientific disciplines.

The growing diversity of scientific fields and stakeholders requires cross-disciplinary dialogue and collaboration between different sectors (e.g. public, private and the laboratory community of DIY biotechnology), scientific disciplines and stakeholders. A broad range of stakeholders will need to develop their capacities to govern both the potential benefits and risks of life sciences research and its applications. Such stakeholders include scientists and their institutions (including research conducted by scientists other than life scientists who use biological knowledge, expertise, data, materials and technologies), funding bodies, publishers, editors, policy-makers and regulators, the private sector and security actors.

As scientific and technological understanding in the life sciences and converging disciplines are advancing, potential safety and security risks have emerged that extend beyond pathogens, life sciences and technologies, and traditional laboratory settings. The rapid pace of advances in the life sciences, the convergence of the life sciences with other scientific disciplines, the diffusion of capacity and knowledge, and the multiplicity of actors and sectors require responsible governance mechanisms and systems that are anticipatory, flexible, responsive and collaborative ([Box 3](#)).

2.2 Identifying and managing potential risks

Research and technologies that have the potential to benefit health and societies also have the potential to be exploited for harmful purposes – a situation referred to as the “dual-use dilemma” (45). This dilemma raises the critical challenge of identifying dual-use research, technologies and knowledge, and then effectively managing the associated risks without hindering the potential benefits for health and society (40).

Two prominent attempts to characterize the security risks stemming from life sciences research were made in two reports from the US National Research Council (NRC) – one in 2004, the other in 2006 (45, 46).⁷ The 2004 report (45) identified seven types of experiments of concern involving microbial agents that would warrant review and discussion before their commencement. The seven types of experiment would demonstrate how to render a vaccine ineffective; confer resistance to therapeutically useful antibiotics or antiviral agents; enhance the virulence of a pathogen or render a nonpathogen virulent; increase the transmissibility of a pathogen; alter the host range of a pathogen; enable the evasion of diagnostic or detection modalities; and enable the weaponization of a biological agent or toxin. Any of those seven types of experiments could also be combined.

Whereas the 2004 NRC report focused on microbial threats and the oversight of research, the 2006 report (46) identified classes of advances that shared characteristics (i.e. common purposes, common conceptual underpinnings and common technical enabling platforms), and outlined a logical framework for assessing the potential for beneficial and destructive applications of new life sciences and technologies. The new technologies were classified into four groups of technologies that seek to acquire novel biological or molecular diversity; generate novel but predetermined and specific biological or molecular entities through directed design; understand and manipulate biological systems in a more comprehensive and effective manner; and enhance production, delivery and “packaging” of biologically active materials. The report recommended adopting a broader perspective of threats beyond pathogenic organisms and toxins. [Box 1](#) lists several reports and tools aimed at identifying or managing dual-use research.

⁷ See also NRC (2002) (47).

A subsequent challenge concerns the difficulty of assessing the benefits and risks posed by dual-use life sciences and technologies, and managing those risks once they have been identified. Over the past decade, several quantitative and qualitative frameworks have been developed for assessing the security risks stemming from the life sciences (*Box 1*). These frameworks vary in terms of drivers, goals and the technologies considered, and in their considerations of intent, risks and benefits, and time horizons and design (48). Few frameworks balance the benefits and risks of dual-use biological research. Assessment of both the benefits and risks of emerging technologies will also be influenced by value judgements and uncertainties, and by societal factors that affect the acceptance of risks and the value placed on benefits (48). Inappropriate application of the life sciences can generate different types of harms, including harms to public health, safety and security; harms to privacy and human rights; harms to the economy; and harms to the environment and biodiversity.

The difficulty of measuring risks and benefits can be illustrated by questions such as “Who benefits?”, “How are benefits and risks distributed?” and “How do we measure risks and benefits, over what time frames, and by what metric or indicator?” Answers to these questions will be influenced by value judgements, uncertainties and societal factors. Hence, analysing the risks and benefits of dual-use life sciences research is challenging. In addition, a risk–benefit analysis can be difficult to perform for basic research and curiosity-driven research, whose long-term societal outcomes and potential future applications might be difficult to anticipate. Focus can be placed on risk assessment and risk management with the exercise of caution (e.g. appropriate use of safe practices, appropriate biosafety equipment and biosecurity measures) in the planning and pursuit of basic and applied life sciences, to minimize risks to health, safety and security (*Table 1*). A pilot exercise on two qualitative frameworks run by the InterAcademy Partnership (IAP) and the US National Academies of Sciences, Engineering, and Medicine (NASEM) concluded that qualitative frameworks are useful for fostering systematic discussions that enable the assessment of security risks; the IAP and NASEM highlighted the need for benefits frameworks (49).

Box 1. Examples of documents and tools for identifying or managing dual-use research, listed by year of publication

- National Research Council. Biotechnology research in an age of terrorism. Washington, DC: The National Academies Press; 2004 (<https://www.nap.edu/catalog/10827/biotechnology-research-in-an-age-of-terrorism>) (45).
- Biorisk management: laboratory biosecurity guidance (WHO/CDS/EPR/2006.6). Geneva: World Health Organization; 2006 (<https://apps.who.int/iris/handle/10665/69390>) (50) (under revision).
- Israel Academy of Sciences and Humanities, Israel National Security Council. Biotechnological research in an age of terrorism. Jerusalem; 2008 (<https://www.academy.ac.il/SystemFiles/21677.pdf>) (51).
- Responsible life sciences research for global health security: a guidance document (WHO/HSE/GAR/BDP/2010.2). Geneva: World Health Organization; 2010 (<https://apps.who.int/iris/handle/10665/70507>) (23).
- Tucker JB. Innovation, dual use, and security. Managing the risks of emerging biological and chemical technologies. Cambridge, Massachusetts & London, England: The MIT Press; 2012 (<https://mitpress.mit.edu/books/innovation-dual-use-and-security>) (40).
- Dual use potential of life sciences research. Code of conduct for risk assessment and risk mitigation. Germany: Robert Koch Institut; 2013 (https://www.rki.de/EN/Content/Institute/Dual_Use/code_of_conduct.html) (52).
- National and transnational security implications of big data in the life sciences. Washington: American Association for the Advancement of Science; 2014 (http://www.aaas.org/sites/default/files/AAAS-FBI-UNICRI_Big_Data_Report_111014.pdf) (53).
- Tools for the identification, assessment, management, and responsible communication of dual use research of concern. USA: National Institutes of Health; 2014 (<https://www.phe.gov/s3/dualuse/Documents/durc-companion-guide.pdf>) (54).
- Scientific freedom and scientific responsibility recommendations for handling security-relevant research. Berlin: German National Academy of Sciences; 2014 (<https://www.leopoldina.org/en/publications/detailview/publication/scientific-freedom-and-scientific-responsibility-2014/>) (55).
- The state of biosafety and biosecurity in South Africa. Pretoria: Academy of Science of South Africa (ASSAf); 2015 (<https://www.assaf.org.za/wp-content/uploads/2015/02/The-State-of-Biosafety-Biosecurity-Report-FINAL.pdf>) (56).
- An efficient and practical approach to biosecurity. Denmark: Centre for Biosecurity and Biopreparedness; 2015 (<https://biosecuritycentral.org/resource/core-guidance-and-recommendations/efficient-and-practical-approach-to-biosecurity/>) (57).
- Risk and benefit analysis of gain of function research: final report. Beverly, MA: Gryphon Scientific; 2015 (<https://osp.od.nih.gov/wp-content/uploads/2015/12/Risk%20and%20Benefit%20Analysis%20of%20Gain%20of%20Function%20Research%20-%20Draft%20Final%20Report.pdf>) (58).

- Recommended policy guidance for departmental development of review mechanisms for potential pandemic pathogen care and oversight (P3CO). Washington: White House Office of Science and Technology Policy; 2017 (<https://www.phe.gov/s3/dualuse/Documents/P3CO-FinalGuidanceStatement.pdf>) (60).
- Koblentz G, Kirkpatrick J, Palmer M, Denton S, Tiu B, Gloss K. Biotechnology risk assessment: state of the field. Editing Biosecurity Working Paper No. 1. Arlington, VA: George Mason University; 2017 (http://jbox.gmu.edu/xmlui/bitstream/handle/1920/11340/Biotech%20Risk%20Assessment_WP1.pdf?sequence=1&isAllowed=y) (48)
- Cummings CL, Kuzma J. Societal Risk Evaluation Scheme (SRES): scenario-based multi-criteria evaluation of synthetic biology applications. PLoS One. 2017;12(1):e0168564 (<https://pubmed.ncbi.nlm.nih.gov/28052080/>) (61).
- Biodefense in the age of synthetic biology. Washington, DC: National Academies of Sciences, Engineering, and Medicine; 2018 (<https://doi.org/10.17226/24890>) (6).
- Canadian biosafety guideline – dual-use in life science research. Ottawa: Government of Canada; 2018 (<https://www.canada.ca/en/public-health/programs/consultation-biosafety-guideline-dual-use-life-science-research/document.html>) (62).
- ISO 35001: Biorisk management for laboratories and other related organisations. Geneva: International Organization for Standardization (ISO); 2019 (<https://www.iso.org/standard/71293.html>) (63).
- Assessing the potential biosecurity risks and benefits of advances in science and technology: results of a pilot exercise using qualitative frameworks. InterAcademy Partnership; 2019 (https://www.interacademies.org/sites/default/files/publication/potential_biosecurity_risks_benefits_iap_web.pdf) (49).
- Outbreak preparedness and resilience. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/337959>) (64).
- Laboratory biosafety manual, fourth edition. Geneva: World Health Organization; 2020 (<https://www.who.int/publications/i/item/9789240011311>) (3).
- Biosafety programme management. Annex 3. Biosecurity risk assessment template. Decision tree to evaluate dual-use potential. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/337963>) (65).
- Safety form. Boston: International Genetically Engineered Machine (iGEM) Foundation; 2020 (https://2020.igem.org/Safety/Final_Safety_Form) (66).
- Bowman K, Husbands JL, Feakes D, McGrath PF, Connell N, Morgan K. Assessing the risks and benefits of advances in science and technology: exploring the potential of qualitative frameworks. Health Secur. 2020;18(3):186–94 (<https://pubmed.ncbi.nlm.nih.gov/32522047/>) (67).
- O'Brien JT, Nelson C. Assessing the risks posed by the convergence of artificial intelligence and biotechnology. Health Secur. 2020;18(3):219–27 (<https://pubmed.ncbi.nlm.nih.gov/32559154/>) (68).

- Culture of biosafety, biosecurity, and responsible conduct in the life sciences – (self) assessment framework. International Working Group on Strengthening the Culture of Biosafety, Biosecurity, and Responsible Conduct in the Life Sciences; 2020 (https://absa.org/wp-content/uploads/2020/02/Culture_of_Biosafety-Biosecurity_Self-Assessment_Framework.pdf) (69), and the accompanying data collection tool – a Microsoft Excel file that can be downloaded (https://absa.org/wp-content/uploads/2020/02/Culture_of_Biosafety-Biosecurity_Self-Assessment_Framework-Template.xlsx).
- A guide to training and information resources on the culture of biosafety, biosecurity and responsible conduct in the life sciences. International Working Group on Strengthening the Culture of Biosafety, Biosecurity, and Responsible Conduct in the Life Sciences; 2021 (https://carpha.org/Portals/0/Documents/Culture%20of%20Biosafety%20and%20Biosecurity%20Guide%20to%20Training%20and%20Information_2021.pdf) (70).
- Dual use research of concern [website]. Washington, DC: United States Department of Health and Human Services; 2021 (<https://www.phe.gov/s3/dualuse/Pages/default.aspx>) (71).
- Dual-use quickscan [website]. Netherlands: Biosecurity Office; 2021 (<https://dualusequickscan.com/>) (72).
- Emerging technologies and dual-use concerns: a horizon scan for global public health. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/346862>) (42).
- Foresight approaches in global public health: a practical guide for WHO staff. Geneva: World Health Organization; 2022 (<https://apps.who.int/iris/handle/10665/359114>) (73).

As the life sciences evolve and intersect with other scientific fields and technologies, the assessment of risks and benefits is becoming more complex and uncertain. Also, in identifying life sciences research and technologies that could cause harm through accidents, inadvertent or deliberate misuse, we need to think beyond specific pathogens, experiments and biology. Assessment frameworks will need to be adapted to encompass evolving risks and benefits. Clearly, there is a need for a comprehensive and integrated framework approach. Foresight approaches offer tools that can inform assessment methodologies designed to deal with the evolving and dynamic diversification of risks. Overall, these approaches provide guidance at the international level on addressing different risks, outline various tools and mechanisms, and serve different stakeholders (*Box 2*).

Box 2. Foresight and biorisk management: role and methods

Foresight offers a systematic approach that can be used to explore and debate complex futures, with an emphasis on decisions and policies in the present that will shape the future. It is an exploratory, deliberative and participatory approach for the early identification of trends or advances in science and technology that may have notable impacts on the future of public health.

Rapid technological changes and emerging technologies transform our societies, with their potential for tremendous benefits for societies and improvements in health; however, they could also result in major economic and societal disruptions. Technological and scientific advancement and innovation are characterized by complex and dynamic interactions, serendipity and inherent unpredictability.

To support the responsible use of the life sciences, foresight can be seen as a systematic way to look at future science, technology and innovation developments and emerging issues, to make better informed decisions and policies. Foresight is not a predictive or forecasting tool; instead, it involves a broad range of actors with diverse perspectives to

inform and support strategic decision-making. Rather than trying to reduce the future to a single definitive prediction, the value of foresight is that it provides alternative perspectives, illuminating a range of options and reducing blind spots in anticipating unintended consequences and emerging challenges.

Foresight can be used to design anticipatory and responsive biorisk frameworks. Multiple scenarios have been developed for this framework (*Annex 1*) to explore different potential futures and to identify practical and robust strategies to address and test the framework against those futures.

Innovation and risks associated with technological developments often emerge at the interface or convergence of various technological fields, as is the case in the life sciences. Foresight involves a wide range of methods; for example, horizon scans, which have been used to monitor advances in science and technology, and identify emerging opportunities and risks (73, 74). The results of a 2021 horizon scan performed by an international group of experts in identifying priority areas to monitor in dual-use research identified 15 priority issues that merit close attention (42).

Another risk that needs to be considered is associated with infodemics, misinformation and disinformation in life sciences research and technologies. An infodemic is an overwhelming amount of information, including misinformation and disinformation, that accompanies an emergency as individuals and communities struggle to separate scientific facts and guidance from manipulative, emotionally charged or inaccurate content (75-77). With increasing digitization – through social media and internet use – information can spread more rapidly. Although this can help to quickly fill information voids it can also amplify harmful messages. Infodemics have manifested themselves in the rapid spread of questions, concerns and misinformation that can affect population attitudes and behaviour harmful to health, from promoting stigma and discrediting science, to promoting alternative, nonrecommended treatment and cures, to politicizing public health programmes and eroding trust in health care personnel and health systems. An infodemic is not only driven by misinformation, it also involves other challenges such as information overload, unsettled science and lack of reliable health information. These challenges can fuel concerns and confusion that undermine outbreak responses, but public health capacity for infodemic management has been limited thus far. Infodemics, misinformation and disinformation can obstruct public health responses and affect decision-making and public policies. In the context of the COVID-19 pandemic, the impact on human behaviour may have hampered public health policy efficacy, leading to suboptimal outcomes (78). Misinformation and disinformation can also directly affect dual-use research and technologies (42), with the risk that scientific activities and research information be misinterpreted or mischaracterized.

Managing an infodemic, and responding to people’s concerns, questions and information needs at the right time, in the right format and through the right channels and services will reduce the harmful effects that circulating misinformation and disinformation may have on public health. In an infodemic, credible, authoritative voices must compete against a plethora of competing information and misinformation packaged to provoke strong emotion in individuals and communities. Knowing which information voids and misinformation to address can be difficult, and requires a methodological approach.

In the context of this framework, understanding concerns, questions, information voids, confusion and circulating narratives (including misinformation and disinformation) can enable better tailored development of guidance and science reporting, and therefore better management of the risk of the scientific process and data being misunderstood, misrepresented

or misused. Anticipating, preventing and managing infodemics is one of the commitments for safe, secure and responsible use of the life sciences ([Section 3](#)) and should be part of biorisk management systems ([Section 5](#)). Addressing this will require a cross-sector approach towards managing infodemics, and the harm that confusion, mistrust, misinformation and disinformation⁸ can have on public health and the health sector.

Multiple stakeholders have different roles and responsibilities in anticipating and preventing the likelihood of infodemics and managing the dissemination of reliable and credible information in ways that are effective, emotionally engaging and able to compete with lower quality information or misinformation. Also, there are competing values at play. Although there is a need to have reliable and credible information, freedom of speech should be maintained, not only as a matter of principle, but because our understanding of what is “accurate” can be modified when minority viewpoints are aired, critiqued and sometimes confirmed. Anticipating and preventing infodemics in life sciences research and technologies is critical for achieving higher effectiveness of public health interventions, and for maintaining and developing trust in science, health systems and health interventions. A positive and proactive approach to credible information sharing and meeting the concerns and needs of populations will contribute to prevent the likelihood that infodemics are harmful to health rather than solely focusing on reactive and counteractive approaches. Some infodemic management interventions are novel and innovative, but all should be evidence based.

The increasing development of large health data sets, research and DNA databases, the digitization of health data and the increasing use of integrated data require biodata to be well managed to ensure that these data are not exploited to cause harm. Biodata for research and development have dual-use potential. Access to data is critical during health emergencies and for health research. At the same time, the risk that data might be misused for harmful purposes requires mechanisms and expertise that ensure these data are kept secure. Safe and secure data management (e.g. through the use of cyberbiosecurity) is an integral part of biorisk management ([Section 5](#)). Addressing these challenges will require a multidisciplinary approach that includes awareness-raising and capacity-building activities.

⁸ See UNICRI (2020) (79).

2.3 Persistent lack of awareness

A chronic and fundamental challenge in biorisk management is a widespread lack of awareness that work in the area of the life sciences could be conducted or misused in ways that result in health and security risks to the public. The lack of awareness is unsurprising, given that biorisks are often overlooked or underemphasized in both educational curricula and on-the-job training. If they are unaware of the potential for misuse and potential malicious application, stakeholders cannot accurately weigh the risks and benefits of proposed research or order. Lack of awareness can also mean that stakeholders are unprepared when new technologies are being introduced as diagnostics, treatments or vaccines. During the introduction of any new technology into the health system, organizational awareness and infodemic monitoring systems need to be set up in ways that are responsive to people's concerns, questions and worries. The lack of such preparation can lead to misinformation and conspiracy theories about technologies that can be difficult to counter.

The lack of awareness can be reinforced by a lack of institutional incentives to attend to safety and security concerns, coupled with ambiguities around the roles and responsibilities of different stakeholders. In addition, there are few opportunities for shared feedback and learning forums for exchange of information on such concerns.

Among stakeholders overall, there is a lack of awareness of biosafety, laboratory biosecurity and research with dual-use potential. Globally, many scientists conducting life sciences research are not trained in biosecurity, not familiar with the BWC (12) and the UNSCR 1540 (17), and not incentivized to devote time and resources to biorisk management. This lack of awareness is even more acute in low- and middle-income countries (LMIC), where it is compounded by a lack of resources. A similar lack of education in biorisk management policies and practices is found among other stakeholders. Thus, although it will take time and resources, any biorisk management system must place a high priority on education, awareness building, and the creation of a culture of individual and institutional investment in biosafety, laboratory biosecurity and oversight of dual-use research.

The scale of the need for awareness raising and education should be understood. Globally, there are millions of life scientists, and it is likely that their numbers will increase in the future with the current biotechnology revolution. Only a small percentage of life scientists are aware of, and have the ability to manage, biosafety, biosecurity and dual-use issues. Improving biorisk management will require resources. Collaborative ambition among stakeholders combined with improvements in awareness raising, education, training, professional development and cultural shifts will be critical to help with meeting the challenge.

Oversight of biosafety, laboratory biosecurity and dual-use research is critical for responsible research, but it depends on the behaviour of individuals and the culture of institutions. Creating an adequate biorisk management framework requires buy-in from all organizational levels, and adequate incentives and resources (including human resources) if all levels are to be able and willing to invest in the creation and maintenance of biorisk management systems.

2.4 Attending gaps in biorisk governance

The deliberate misuse of biological agents and toxins for harmful purposes is formally prohibited by international law, through the 1925 Geneva Protocol (11), the 1972 BWC (12) and the 1993 CWC (13).^{9,10}

The 1925 Geneva Protocol prohibits “the use in war of asphyxiating, poisonous, or other gases and of all analogous liquids, materials or devices (...) [and] the use of bacteriological methods of warfare” (11). However, the Geneva Protocol, which is considered to have entered customary international law and is therefore binding even on States that are not parties to it, only prohibits the use of such weapons, not their possession. Moreover, because it was considered by many States Parties as a no-first-use agreement, a comprehensive prohibition of biological and chemical weapons came to be considered necessary (22). The 1972 BWC, which is the first treaty to ban an entire category of weapons (27), complements the prohibition of the use of biological weapons of the 1925 Geneva Protocol and bans the development, production, acquisition, transfer, stockpiling and use of biological and toxin weapons. States Parties to the BWC have adopted national laws and regulations to implement these obligations under this treaty. Some countries have put into place policies and measures to govern dual-use life sciences research.¹¹ Through the intersessional programme, the BWC, which is supported by the Implementation Support Unit, plays a critical role in discussing and reaching common understandings on issues associated with the governance of dual-use life sciences research. Moreover, the confidence-building measures submitted by States Parties are aimed to prevent or reduce the occurrence of ambiguities, doubts and suspicions and to improve international cooperation in the field of peaceful biological activities (83). However, the BWC lacks verification mechanisms for compliance with its provisions.¹² The 1993 CWC, which prohibits the development, production, acquisition, stockpiling, retention, transfer or use of chemical weapons, also includes under its remit toxic substances and bioregulators (84).¹³

⁹ Moreover, States Parties to the 1977 Convention on the Prohibition of Military or Any Other Hostile Use of Environmental Modification Techniques (ENMOD) undertake “not to engage in military or any other hostile use of environmental modification techniques having widespread, long-lasting or severe effects as the means of destruction, damage or injury to any other State Party” and “not to assist, encourage or induce any State, group of States or international organization to engage in activities contrary to the provisions of paragraph 1 of this article” (80).

¹⁰ Several countries have also adopted policies coordinating their national export controls of dual-use goods to prevent the proliferation of chemical and biological weapons. These include the Wassenaar Arrangement (81) and the Australia Group (82).

¹¹ See also Appendix E Examples of activities across the governance landscape (27).

¹² Review conferences of the BWC are held every 5 years to evaluate the impact of science and technology advances on the Convention and to ensure that the Convention remains relevant and effective. Moreover, annual meetings of experts and States Parties are being held to share information on specific topics.

¹³ See footnote 2.

Furthermore, in accordance with the UNSCR 1540 (17), all States are required to adopt and enforce effective laws and measures to prevent the proliferation of nuclear, chemical or biological weapons and their means of delivery, including by establishing appropriate controls over related materials to non-State actors.¹⁴

Other communities (e.g. academia and scientific bodies, organizations or councils, research institutions, funders, publishers, editors, the private sector, and regional and international organizations) have been working towards the development of measures to reduce the risks of accidents, inadvertent and deliberate misuse of the life sciences (*Section 4*).

Despite these endeavours, countries continue to have gaps in their biorisk management. Although there is an international treaty against biological weapons, the BWC and norms for the responsible conduct of research (85), additional international guidance for Member States and other stakeholders will practically assist its implementation. Such guidance should cover ways to identify, prevent and mitigate risks related to life sciences research and technologies. In general, countries have stronger risk mitigation measures for biosafety than for laboratory biosecurity, and often lack oversight of advanced life sciences research to mitigate potential biorisk concerns. Biorisk management is even less common for research in fields adjacent to the life sciences, such as technology development that leverages biology, and science and technology development hubs that are not traditional laboratories. Critically, biotechnology is rapidly advancing and converging with other technologies, changing the potential risk landscape. Existing strategies may not be adequate to address the risk posed by these technologies; hence, new proactive, innovative, holistic frameworks are needed.

Another core problem and overarching gap is the paucity of national legislation, regulations or guidelines for governing biorisk management and its implementation. Increasing both awareness and incentives is hindered by a lack of top-down activities or formal national legislation, regulations and policies. Although both top-down and bottom-up approaches are needed for a holistic system, development of bottom-up approaches requires creation of awareness or incentives from the top.

¹⁴ According to UNSCR 1540 (17), "related materials" are "materials, equipment and technology covered by relevant multilateral treaties and arrangements, or included on national control lists, which could be used for the design, development, production or use of nuclear, chemical and biological weapons and their means of delivery".

The governance of biorisks varies considerably across countries. It includes both formal mechanisms (e.g. international laws, national legislation and regulations, and mandated national and institutional oversight) and informal mechanisms (e.g. self-governance, awareness raising among scientists, codes of conduct, institutional oversight and international guidance). Some countries have chosen particular schemes to implement biorisk management systems; in some cases, tools from several systems have been adapted to address different risks. Other countries have biosafety measures in place but do not have any national governance framework for oversight of biosecurity or dual-use research. Whether the components of biorisk management are assessed individually or collectively, biorisk management practices and governance structures vary greatly across regions and countries, and in many countries they may be inadequate at most levels – individual, institutional, national, regional and international. Agreed definitions and an integrated approach to biorisk management in the life sciences research enterprise will strengthen global health security.

2.5 Updating terminologies and framing

In terms of reducing biorisks associated with research and technology development, Member States and other stakeholders may understandably be confused about how to define and govern “risky” practices. The types of “risky” research, experiments, materials and information may depend on contexts and can include gain-of-function research and research with dangerous pathogens. Yet high-risk life sciences research extends to other emerging areas and converging technologies with dual-use potential (*Section 2.1*). Hence, this framework adopts the umbrella term of “biorisk management” as an overarching framework for discussing the full spectrum of risks associated with the life sciences research enterprise, recognizing that risk mitigation measures may address multiple types of risk.

Biorisk management relies on three core pillars: biosafety, laboratory biosecurity and the oversight of dual-use research. In the context of this framework, the meanings of these terms are as outlined below:¹⁵

Biosafety

Biosafety refers to the containment principles, technologies, measures and practices that are implemented to prevent unintentional exposure to biological agents or their inadvertent release. The fourth edition of the WHO Laboratory biosafety manual takes a risk-based and evidence-based approach to biosafety (3). It emphasizes the importance of a safety culture to ensure a safe workplace where adequate measures are applied to minimize the likelihood and severity of any potential exposure to or release of biological agents (3).

¹⁵ These definitions are consistent with how these terms are currently used in various publications from WHO (3, 23) and the International Organization for Standardization (ISO) (63).

Laboratory biosecurity

Laboratory biosecurity refers to the principles, technologies, measures and practices that are implemented for the protection, control and accountability of biological agents, data or equipment, biotechnologies, skills and information related to their handling. Biosecurity aims to prevent their unauthorized access, loss, theft, misuse, diversion or release. Addressing laboratory biosecurity risks in many ways parallels and complements biosafety risk management. Effective biosafety practices are the foundation of laboratory biosecurity, and biosecurity risk control measures must be performed as an integral part of an institution's biosafety programme management (3).

Oversight of dual-use research

Oversight of dual-use research refers to formal and informal measures (e.g. legislation, regulations, policies, training, codes of conduct, awareness-raising activities and other tools and mechanisms) put into place by different stakeholders to prevent and mitigate the risks stemming from research with dual-use potential. Dual-use research is conducted for peaceful and beneficial purposes, but has the potential to produce knowledge, information, methods, products or technologies that could also be intentionally misused to endanger the health of humans, nonhuman animals, plants and agriculture, and the environment.

However, there are no universal definitions of biosafety, biosecurity and dual-use life sciences. These terms have gained specific meanings within different disciplines, countries, languages and international treaties (86). For example, in the context of environmental protection, biosafety is associated with the potential impact of GMOs on biodiversity. There are instances where biosafety principles are applied for deliberate releases, as is the case for living modified organisms (LMOs) under the Cartagena Protocol on Biodiversity; LMOs could have both positive and negative impacts for health, environment and safety depending on the application. In the context of agriculture, biosecurity is associated with preventing pests, diseases, zoonoses, invasive alien species and GMOs from harming animal and plant health. Challenges arise when terms are interpreted differently by stakeholders. A further complication is that these terms translate differently in different languages; also, in some languages, a single word denotes both biosecurity and biosafety. Therefore, it is incumbent on individuals and institutions to clearly define these terms and to be aware that alternative definitions may be used by other stakeholders.

There is a growing recognition that the ways in which biosafety, biosecurity and dual-use research have traditionally been defined in the context of life sciences research needs to be updated. For example, biosafety is typically discussed in the context of laboratory operations – hence the WHO *Laboratory biosafety manual* (3) and the US *Biosafety in medical and microbiological laboratories* (87) – but that is too narrow a construction. WHO’s supplemental monograph on biosafety during an outbreak focuses on the collection and handling of biomedical samples taken from patients (3). Practices for safely collecting samples from wild and domesticated animals that may be infected with a zoonotic pathogen should also be considered within the biosafety realm, but are often overlooked and are therefore underdeveloped (88), even though large-scale efforts to collect thousands of viral samples to identify novel zoonoses and potential pandemic pathogens have been associated with accidental exposure and release (89).

The traditional focus of laboratory biosecurity was on preventing unauthorized personnel from gaining access to biological agents in a laboratory; however, biosecurity increasingly includes measures to address so-called insider threats and measures needed to reduce the risks of unauthorized access, theft or diversion of materials and information from places not traditionally thought of as a laboratory (e.g. DIY research spaces, private or non-profit entities or manufacturing facilities). In addition, there is a growing recognition of cyber threats to the life sciences enterprise, including hospitals, biomedical research institutions, genomic databases, biotechnology companies and facilities that manufacture medical countermeasures, which can cause physical disruption or damage, or can compromise confidential or proprietary information.

The term dual-use has different meanings. It can be understood as items (e.g. materials, information and technologies) that can be used for both civilian and military applications (90), or it can refer to the features (both tangible and intangible) of a technology that enable it to be applied to both hostile and peaceful ends with little or no modification (91, 92). In the life sciences, dual-use research raises the challenge of mitigating the risks while harnessing the power and promoting the diffusion of technologies for global health and society. In the context of this framework, dual-use research refers to life sciences research that is conducted for peaceful and beneficial purposes but has the potential to produce knowledge, information, methods, products or technologies that could also be intentionally misused to endanger the health of humans, nonhuman animals, plants and agriculture, and the environment.

The term dual-use research can be limiting when policy implementation is scoped around a narrow set of concerns. First, in practice, the term has often been focused primarily on mitigating the risk of deliberate misuse of high-consequence pathogens used in biological research. As such, it fails to adequately acknowledge risks presented by a broader set of fields of research involving the life sciences that do not focus on pathogens (e.g. neurosciences (93) and synthetic biology); risks presented by techniques, platforms and practices that facilitate research and development (e.g. genome editing and vaccine development platforms); and scientific fields adjacent to and converging with the biological sciences (e.g. AI, automation, bioinformatics, chemistry and nanotechnology) (94). Second, the term dual-use fails to reflect the fact that technologies can have different functions and multiple applications (93). Third, traditional concepts of dual-use research do not account for the possibility that multiple forms of misuse (e.g. reckless, negligent and deliberate) may stem from the same research.

Studies of the terms dual-use and dual-use dilemma have emphasized problems with and the limits of these concepts (95). For example, different understandings of the term dual-use can lead to the creation of different governance mechanisms (96). Also, definitions of dual-use research focus on the potentially devastating consequences for humans, nonhuman animals, plants and agriculture, and the environment in terms of health impact (e.g. poisoning and toxicity), but it is increasingly clear that advances in the life sciences and associated fields can have dramatic effects for humans in areas such as privacy and human rights.

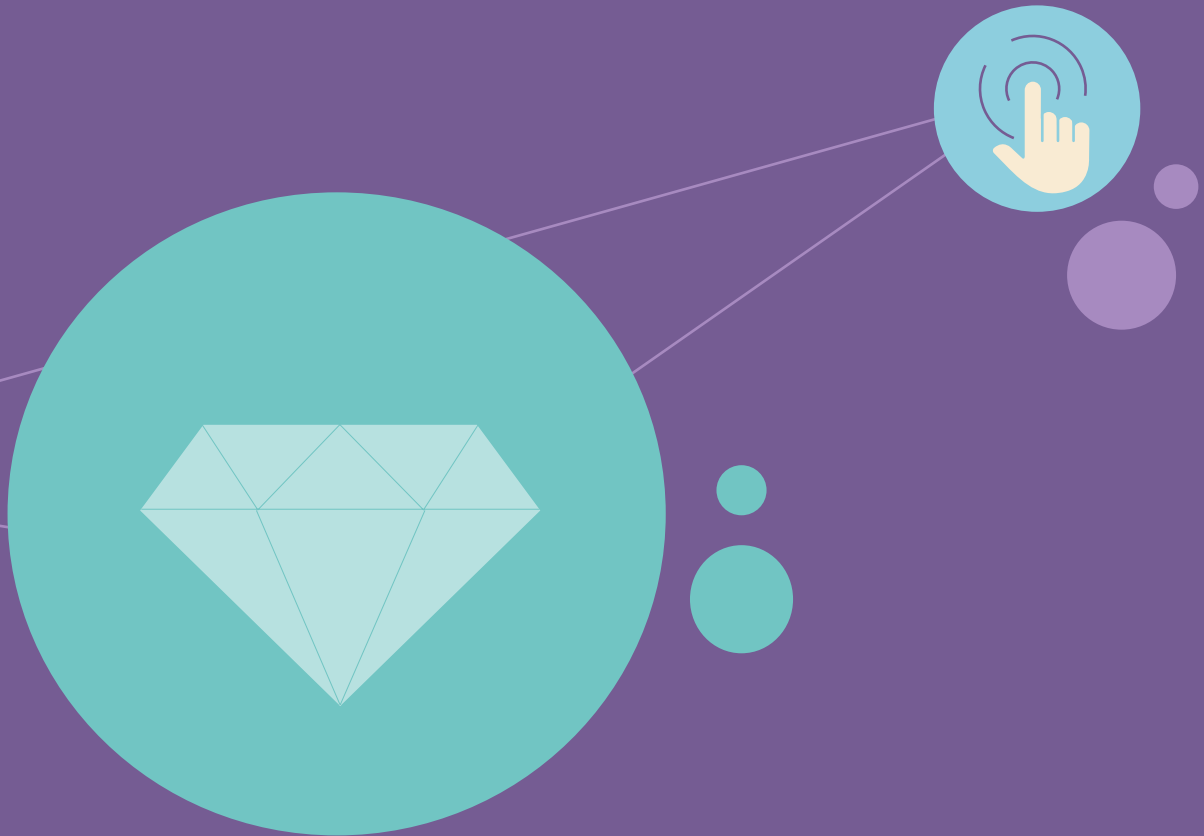
Beyond the problem of definitions, the way in which dual-use is framed and approached is critical. An emphasis on the responsible conduct and use of the life sciences could enable greater involvement from relevant communities and mitigate concerns about additional measures or limitations on research (*Section 1.3*). This framework seeks to approach the governance of biorisks through the promotion of safe, secure and responsible life sciences research and technologies, while harnessing the power of science and innovation to achieve health for all.

The scenarios in *Annex 1* and the three case studies in *Annex 2* illustrate some of the challenges and gaps in the governance of biorisks, and put forward some elements of biorisk management that merit further consideration.



3. Section 3

Values and principles to guide governance of biorisks



This section and [Section 4](#) provide key considerations for addressing the challenges and gaps identified in [Section 2](#). This section identifies the aspects of good governance of biorisks, and outlines the values and principles, and their associated commitments. The values and principles that underpin the framework should guide the development and implementation of effective biorisk management policies by Member States and the actions of relevant stakeholders.¹⁶ Moreover, given that countries and stakeholders have different needs and starting points, common values and principles are critical to guide decision-making.

¹⁶ Section 3 directly draws on the report developed by the WHO working group on values and principles (not published) and on WHO (2022) (38).

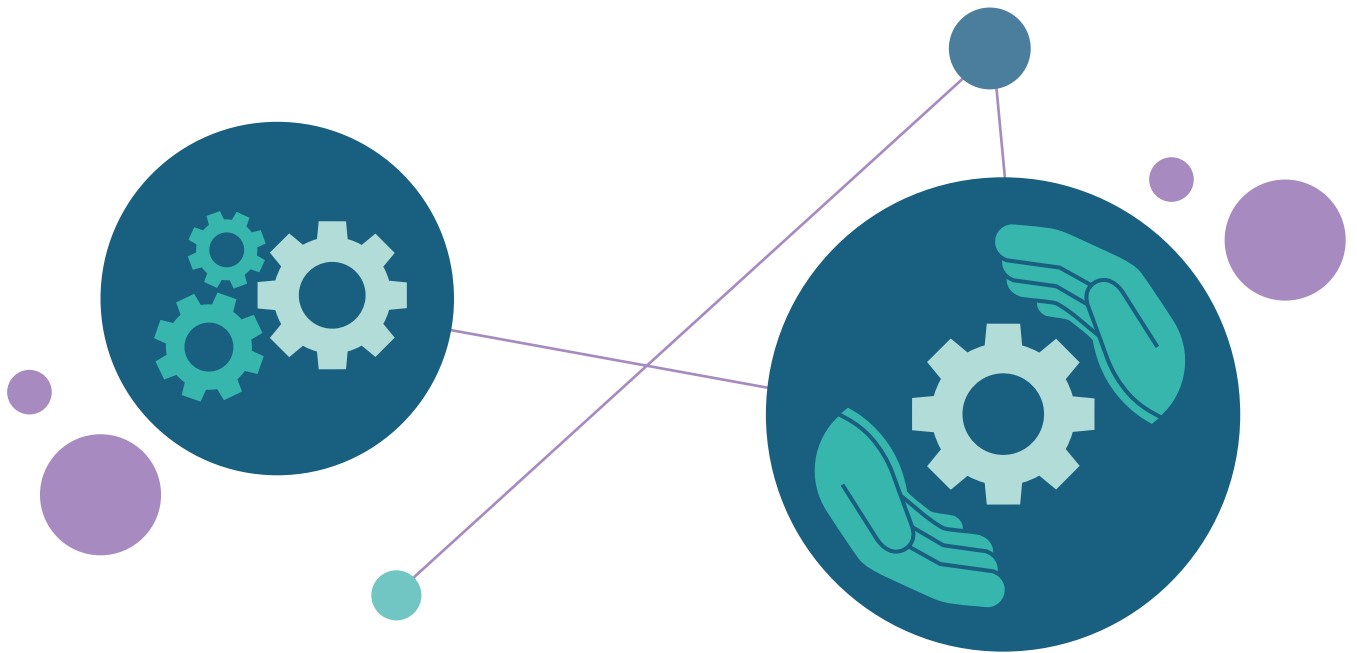
3.1 Governance for the responsible use of the life sciences

This framework understands governance as “... the norms, values and rules of the processes through which public affairs are managed so as to ensure transparency, participation, inclusivity and responsiveness. Governance also represents the structures and processes that are designed to ensure accountability, transparency, responsiveness, adherence to the rule of law, stability, equity and inclusiveness, empowerment, and broad-based participation”.¹⁷

Governance includes both formal mechanisms (e.g. international laws, and national legislation and regulations) and informal mechanisms (e.g. ethical, social and professional norms, industrial norms, publishers’ review processes, funding bodies’ measures, liability insurances, practices associated with self-governance, education, training and codes of conduct). Moreover, governance “includes forces to shape the direction and conditions of research and practice, such as well-crafted public and private funding priorities and conditions” (34).

Governance systems and mechanisms for biorisks will depend on context. Member States vary in terms of level of resources, regulatory environments, risk tolerance and types of research conducted; thus, it is not possible or appropriate to have a one-size-fits-all approach to governance in this area. Also, Member States will start from different points (e.g. with or without governance systems in place, and with or without resources) and their priorities will differ over time.

¹⁷ Section 3.1 draws on the definition of governance put forward by the report *Human genome editing: a framework for governance* (34), and builds on its key considerations associated with the good governance of new and emerging technologies.



Governance of biorisks requires the involvement of all actors associated with the life sciences, including those in charge of its funding, development, publication and applications. Each actor and Member State will need to decide which measures are most appropriate and relevant, according to their own national circumstances and contexts. Sustained and engaged leadership is essential at all levels (governmental through institutional) to ensure appropriate management of biorisks.

Good governance for the responsible use of the life sciences also entails the anticipation of risks and encourages the responsiveness of governance systems (97). As the life sciences evolve and the landscape of risks changes, governance systems need to establish flexible, proactive and enduring frameworks that include iterative processes to regularly re-evaluate the new ways in which life sciences may create risks.

The 2021 WHO publication *Human genome editing: a framework for governance* (34) identifies several key elements for the good governance of new and emerging technologies, which can apply to the good governance of biorisks:

- “Good governance is an iterative, ongoing process that includes mechanisms for regular revision in light of technical, practical and ethical developments and changes in societal views and values. Ideally, good governance is proactive, not only reactive.”
- “Good governance promotes public confidence by ensuring that choices are made in ways that are transparent and inclusive; and it includes means to hold policy-makers accountable for those choices. As needed, good governance also has mechanisms to handle non-compliance with formal governance mechanisms.”
- “Good governance requires access to adequate resources, capacity and technical knowledge to educate, engage and empower members of the scientific, medical and health care communities as well as the public. (...)”
- “Good governance is value-based and principle-driven. It promotes public trust by ensuring public values and viewpoints are carefully considered as part of the policy-making process.”

3.2 Values and principles to guide the governance of biorisks

The governance of biorisks involves specific tools and mechanisms to mitigate risks (*Section 4*); however, strategies to manage biorisks inevitably entail judgements about values and different levels of societal acceptance of risks and uncertainties (*Section 2*).

Therefore, this framework identifies a common set of values and principles that are viewed as “touchstones” for considered ethical judgements to support the development and implementation of effective mechanisms for biorisk management. In addition, because there is no single approach for the effective governance of biorisks (*Section 2*), the values and principles highlight why governance of biorisks is necessary and how it can be achieved through a set of commitments (*Table 1*).

The values and principles serve as a reminder for decision-makers about the beliefs that are important to individuals and organizations, and that should guide decision-making, taking into consideration a wide range of contextual factors. They also underline the need for the scientific community and other stakeholders associated with the life sciences to adhere to high scientific and ethical standards, to ensure that life sciences research and developments are used for the betterment of humans and the planet’s biodiversity, ecosystems and environments. The values and principles are intended to motivate and strengthen ethical and responsible practice, and to guide the policies and actions of Member States and other stakeholders.

The values and principles are intended to:

- delineate the ethical commitments that should guide scientists and the scientific community;
- encourage the use of ethical commitments as an anchor for policy and a community of practice that is aligned with recognized (international) standards, best practices and good governance; and
- serve as a common and unifying language among stakeholders when social, cultural and religious beliefs and ethical values diverge.

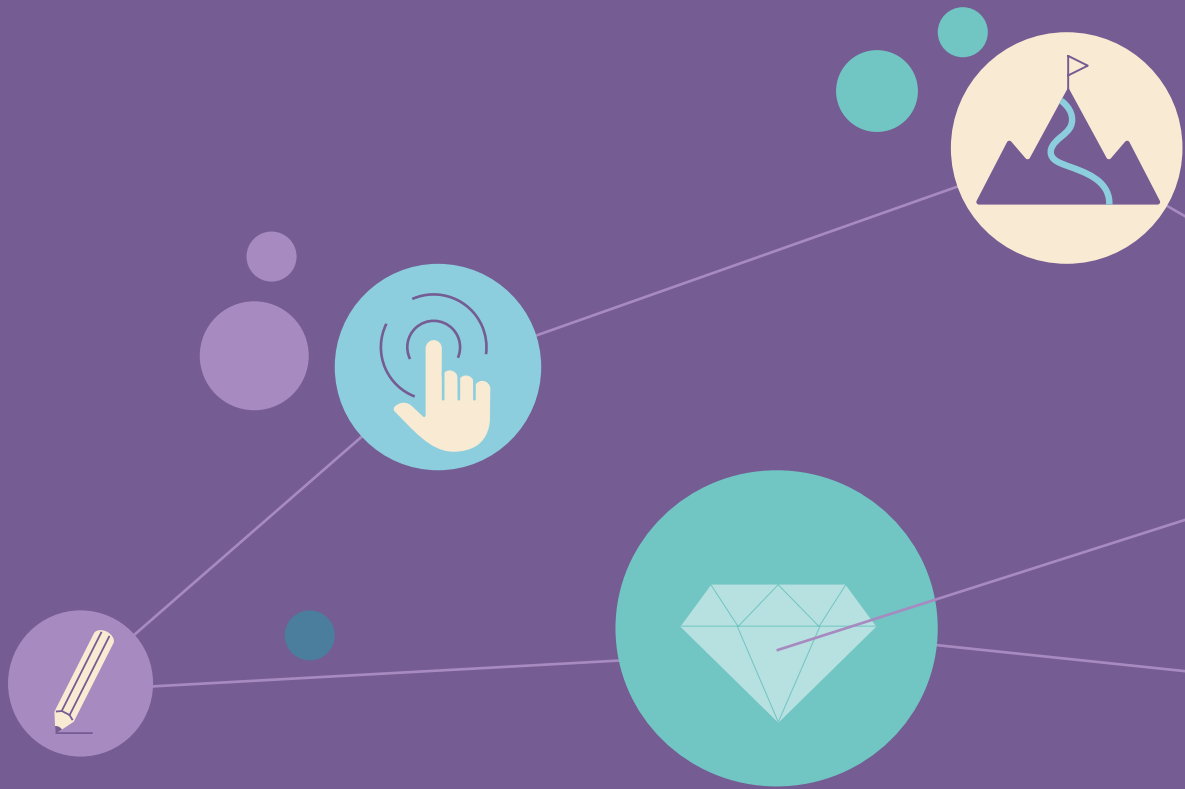
The framework draws on the values and principles and the commitments listed in [Table 1](#), which are based on the set of values and principles identified by the 2021 WHO publication *Human genome editing: a framework for governance* (34). The values and principles listed are not discrete – they overlap where appropriate. The overall goal of this common set of values and principles is that life sciences research and developments be used for the betterment of humans and the planet’s biodiversity, ecosystems and environments. However, these values and commitments may be adapted according to specific circumstances and contexts. Moreover, as the WHO publication *Ethics and governance of artificial intelligence for health* (10) underlines, “In many situations, multiple ethical considerations are relevant and require weighing up and balancing to accommodate the multiple principles at stake. An ethically acceptable decision depends on consideration of the full range of appropriate ethical considerations, ensuring that multiple perspectives are factored into the analysis and creating a decision-making process that stakeholders will consider fair and legitimate”.

Table 1. Values and principles for safe, secure and responsible use of the life sciences

Values and principles	Associated commitments
Health, safety and security	<ul style="list-style-type: none"> - Use knowledge, materials and skills from basic and applied life sciences for peaceful purposes and for the betterment of humans and the planet's biodiversity, ecosystems and environments. - Use appropriate biosafety and biosecurity measures to prevent knowledge, materials and skills from the life sciences from causing harm so that we may live together peacefully. - Preserve biodiversity where possible, both as a means to promote health, safety and security and as an intrinsic value.
Responsible stewardship of science	<ul style="list-style-type: none"> - Pursue rigorous, evidence-based basic and applied life sciences to generate ideas, knowledge, data, products or technologies for peaceful purposes and for the betterment of humans and the planet's biodiversity, ecosystems and environments. - Exercise caution (e.g. appropriate use of safe practices, appropriate biosafety equipment and biosecurity measures) in planning and pursuing basic and applied life sciences in order to minimize risks to health, safety and security. - Identify, manage and mitigate reasonably foreseeable potentially harmful consequences of basic and applied life sciences as a result of accidental, inadvertent or intentional actions by assessing, through a multidisciplinary review process, whether: <ul style="list-style-type: none"> » the identified risks are proportionate to the potential benefits of the research; » less risky forms of research could be equally beneficial; and » modifying the research design or the dissemination and publication plans (as the research proceeds or after the research has been completed) is advisable. - Develop and support policies (including laws, regulations, standards, guidelines, best practices, codes of ethics, research review processes, training and education) at all levels of governance that are specific to basic and applied life sciences which could result in harm to health, safety or security. These policies should reflect the community's values, priorities and risk-taking strategies. - Develop and support ethical practices (with particular attention to issues of intent, integrity and conflicts of interest) to align the processes and outcomes of basic and applied life sciences with societal values, needs and expectations. - Stay informed of current policies and associated best practices for safe, secure and responsible basic and applied life sciences; educate stakeholders about these policies and practices; and contribute time and expertise to improving relevant policies and practices. - Align incentive structures and rewards with these guiding values and principles.

<p>Integrity</p>	<ul style="list-style-type: none"> – Uphold the integrity of the scientific process by generating and responsibly communicating high-quality information (e.g. ideas, knowledge and data), in sufficient detail to permit its reproduction and careful peer review to identify and effectively mitigate biosafety and biosecurity risks. – Counter the dissemination of information that misinterprets or mischaracterizes ideas, knowledge and data, with particular attention to issues of authorship as well as fabrication and falsification of data. – Report possible illegal, unethical or unsafe basic and applied life sciences to relevant institutional, national, regional and international authorities.
<p>Fairness</p>	<ul style="list-style-type: none"> – Ensure fair dealings in conducting basic and applied life sciences, including benefit-sharing (which includes sharing research benefits, research skills and research capacity). – Develop and implement fair processes for the confidential reporting and investigation of possible illegal, unethical or unsafe basic and applied life sciences in pursuit of fair outcomes. These tools and mechanisms should provide appropriate support and protection for both those who report concerns and those alleged to have engaged in illegal, unethical or unsafe activities.
<p>Openness, transparency, honesty and accountability</p>	<ul style="list-style-type: none"> – Use open, transparent, honest and accountable processes to share relevant information about biosafety and biosecurity risks with: <ul style="list-style-type: none"> » the scientific community, including project managers, funders, editors and publishers; » biosafety officers, security officials, regulators, institutional and other authorities; and » civil society networks. – Make scientific information (e.g. ideas, knowledge and data) accessible is essential for understanding health challenges, to develop new solutions and to ensure that decisions are based on the best available evidence (98). On rare occasions, an assessment may conclude that wide dissemination (including publication) would pose a safety or security threat, in which case a decision may be taken that wide dissemination should be curtailed. Thus, manuscripts might have to be modified before publication or not published in full (with this information duly noted in the publication, consistent with a commitment not to intentionally mischaracterize or falsify ideas, knowledge and data). – Hold scientists and the scientific community accountable for the design and pursuit of basic and applied life sciences. Carefully consider the potential consequences of basic and applied life sciences. – Conduct regular audits to ensure compliance with relevant policies for eliminating or minimizing biosafety and biosecurity risks.

Inclusiveness and collaboration	<ul style="list-style-type: none"> - Actively involve people in social science and humanities disciplines in the design and pursuit of basic and applied life sciences, consistent with the recognized value of interdisciplinary research. - Carefully consider perspectives on basic and applied life sciences that are based on different social, cultural and religious beliefs, ethical values, organizational sectors (e.g. academia, government and industry), experiential knowledge and skill sets. - Adopt an international outlook, including consultation, sharing, negotiation, coordination and related forms of active engagement (e.g. programmes for awareness raising and education) with other countries and the wider international community. - Practise basic and applied life sciences in a manner that invites collaborative ambition and work.
Social justice	<ul style="list-style-type: none"> - Consider the needs (and aspirations) of all, and ensure that different groups have adequate, well-balanced and equitable access to the potentially beneficial outcomes of basic and applied life sciences. - Provide scientists in LMIC with equitable access to relevant research training and capacity-building. - Include and empower scientists in LMIC in both the pursuit and governance of basic and applied life sciences.
Intergenerational justice	<ul style="list-style-type: none"> - Protect and promote the health, safety and security of humans, nonhuman animals, plants and agriculture, and the environment by respect for past generations and for the benefit of future generations. These responsibilities include: <ul style="list-style-type: none"> » engaging with the potential consequences of one's actions; » pursuing life sciences of potential benefit to future generations; » managing and mitigating any harms that might accrue to future generations; and » ensuring that biodiversity, ecosystems and environments are preserved where possible.
Public education, engagement and empowerment	<ul style="list-style-type: none"> - Educate civil society networks and publics about the potential benefits, potential harms, limitations and capabilities of basic and applied life sciences in ways that balance competing influences and demands. - Engage civil society networks and publics in deliberations about possible future uses (and potential accidental, inadvertent and intentional misuses) of basic and applied life sciences. - Empower civil society networks and publics by enhancing participatory governance and promoting collaborative ambition to promote trust and strengthen global solidarity in support of health, safety and security.



4. Section 4

Tools and mechanisms for the governance of biorisks



Governance mechanisms for the responsible use of the life sciences should be guided by values and principles (*Section 3*) that are subsequently put into practice through tools and mechanisms for managing biorisks. This section outlines the elements of biorisk governance and considerations for creating a comprehensive and integrated governance framework. Examples of tools and mechanisms to manage biorisks are identified and arranged according to the stakeholders who have responsibilities for such governance.¹⁸

¹⁸ Section 4 draws directly on the report developed by the WHO working group on tools and mechanisms for biorisk management (unpublished) and on WHO (2022) (38).

4.1 Elements of biorisk governance

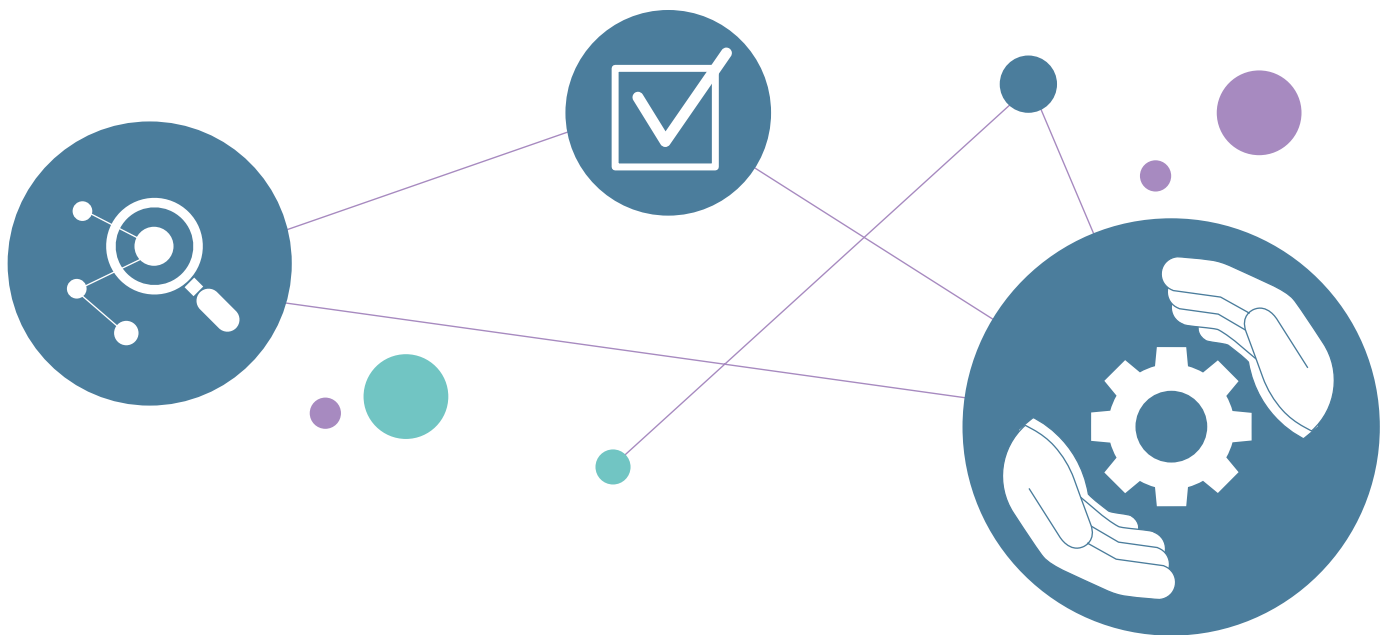
Effective and robust biorisk governance is multifaceted and includes multiple goals, multiple stakeholders and different governance tools and mechanisms, as outlined below:



- a. The *multiple goals* include reducing biosafety incidents and accidents; reducing biosecurity breaches; enabling early detection of biosafety and biosecurity breaches; reducing future opportunities for malicious misuse of research, tools and knowledge; enabling rapid response to biosafety incidents, accidents and biosecurity breaches; and increasing information exchange and learning. Robust biorisk governance systems can also include features such as minimizing undue burdens and costs; having high feasibility and applying a validated or tested approach; managing liability and reputational risks; and strengthening confidence in the life sciences.



- b. The *multiple stakeholders* are those that are best positioned to achieve various goals. These include scientists, technicians, academic institutions, public health and medical microbiology research institutions, commercial research companies, standard setters, funders of research, insurers, editors, publishers and scientific societies. Member States and governments are critical for reinforcing, resourcing and requiring biorisk management options among diverse stakeholders.

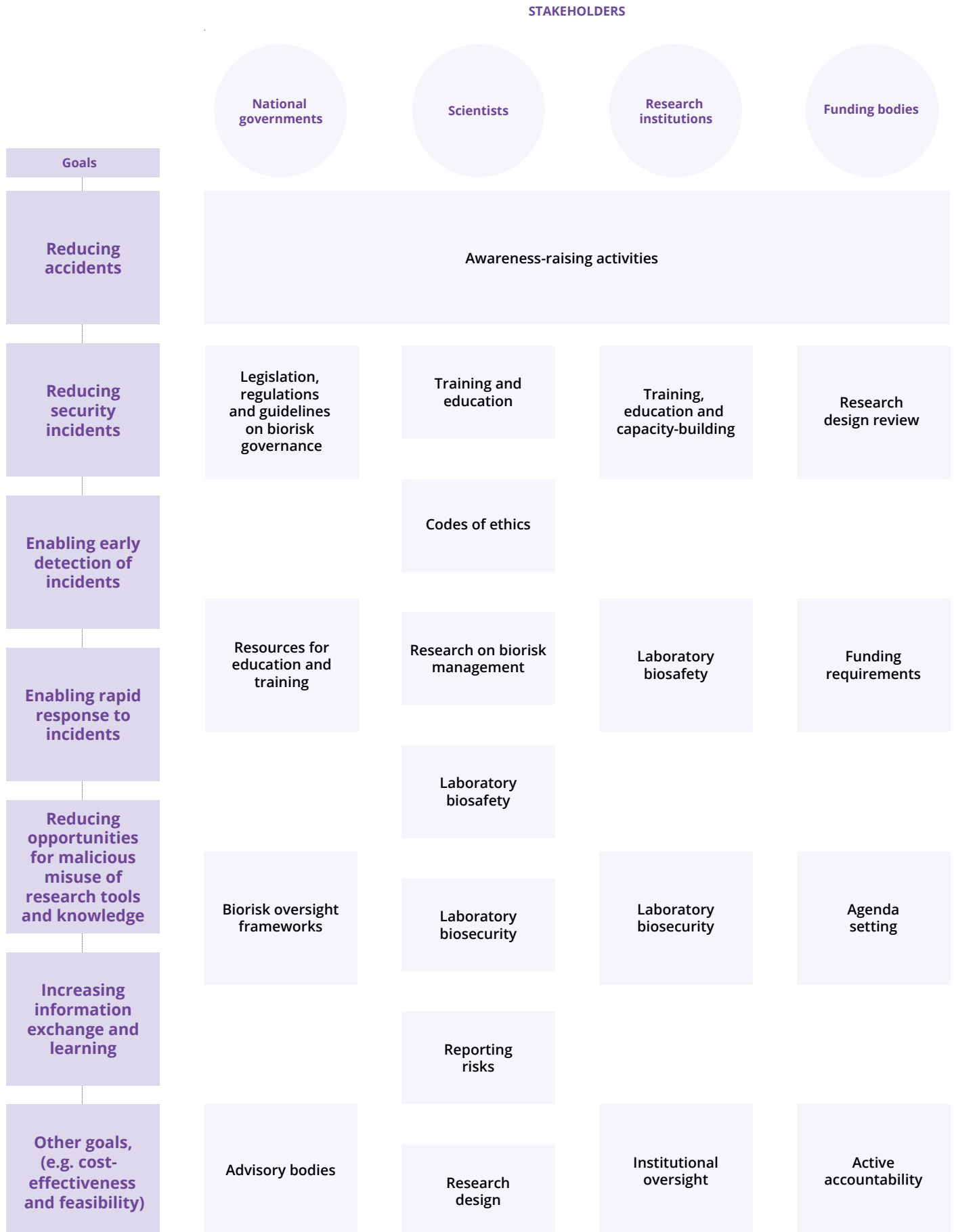


- c. *Different governance tools and mechanisms* are needed to achieve diverse goals and engage different stakeholders. They include laws and regulations, standards, guidelines, best practices, codes of ethics, research review processes, awareness-raising activities, training and education. Tools and mechanisms will vary in their levels of formality, incentives and enforcement (self-governance versus mandatory requirements). Some tools and mechanisms can apply to a range of goals and stakeholders (e.g. training and education can be developed by different stakeholders), whereas others can apply to one or two goals and stakeholders (e.g. laws are developed by governments but they can apply to different goals). The tools and mechanisms chosen will depend on the particular stakeholders, goals and contexts, but should be complementary and mutually reinforcing (*Table 2*). These tools must cohere (99) and the governance approaches must be adaptable to enable innovations in both policies and practices (101, 102).

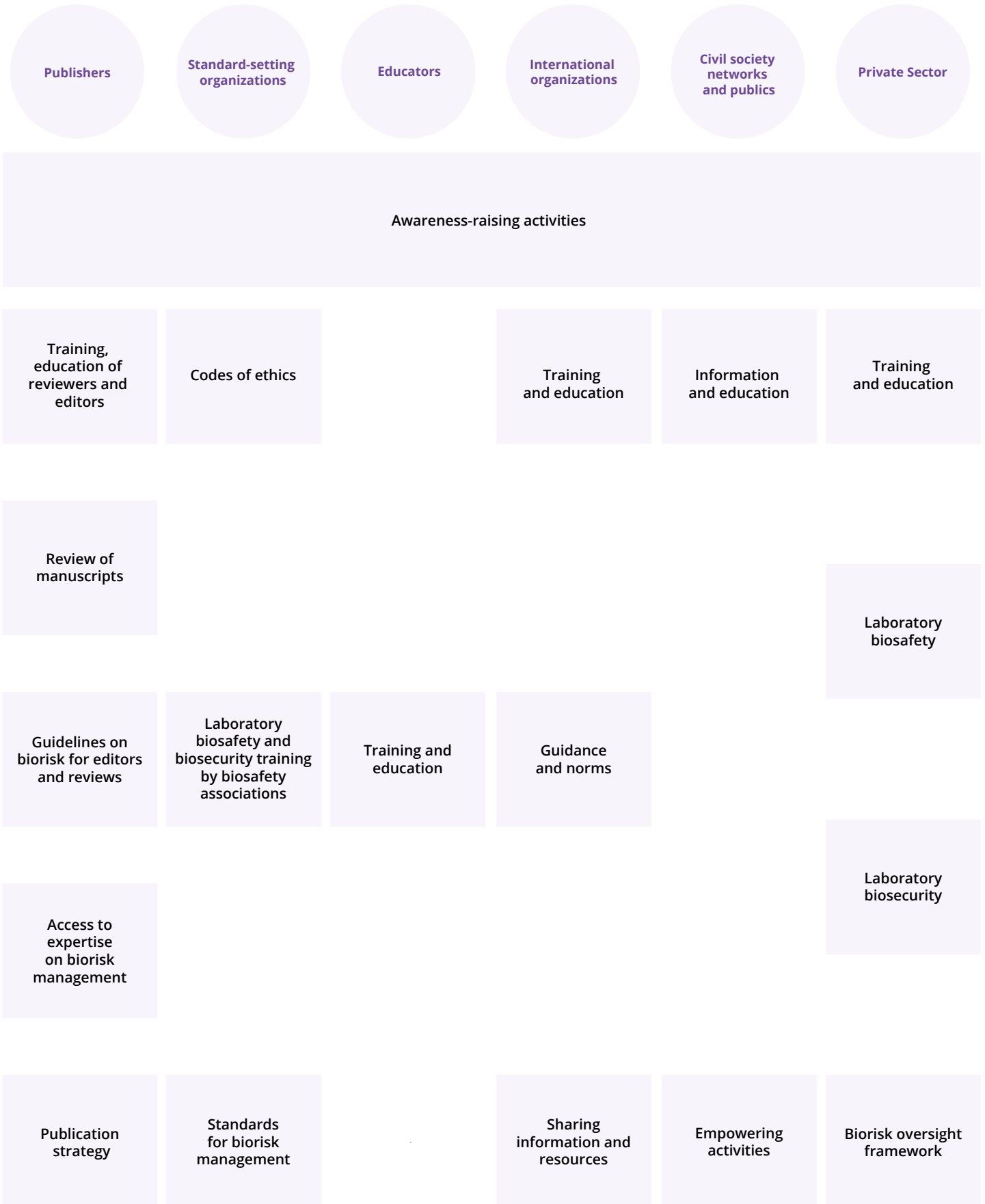
Table 2¹⁹ illustrates examples of biorisk governance tools and mechanisms that can be developed and implemented by various stakeholders and used to reinforce different goals.

¹⁹ Chart adapted from the synthetic genomics options for governance report (100) and from the WHO working group on tools and mechanisms for biorisk management (unpublished).

Table 2. Examples of tools and mechanisms of biorisk governance



STAKEHOLDERS



4.2 A comprehensive governance approach to biorisk management

Biorisk management depends on (i) the values, principles and training of the scientists directly involved in research (the research culture); (ii) active management of biosafety and laboratory biosecurity risks by institutions; and (iii) the government initiatives that set out the responsibilities and obligations of individuals, institutions and other relevant stakeholders (e.g. guidance or legislation). An ultimate vision for success for biorisk management would be that life sciences knowledge, materials and skills are used for peaceful purposes and for the betterment of humans and the planet's biodiversity, ecosystems and environments.

A comprehensive governance approach to biorisk management will include a range of governance tools, mechanisms as well as stakeholders at all levels (individual, institutional, national, regional and international) ([Section 4.1](#)). Simple frameworks can be helpful in assessing which combinations of approaches taken by different stakeholders can best achieve several goals and can be adapted across different organizational contexts (see Table 3 for an illustrative example).

Table 3. An illustrative framework for systematically evaluating tools and mechanisms towards a comprehensive governance approach for biorisk management.

GOALS	Stakeholder A (e.g. scientific societies)	Stakeholder B (e.g. national governments)	Stakeholder C (e.g. funding bodies)
	Tool (e.g. codes of conduct)	Mechanism (e.g. oversight and reporting requirements)	Mechanism (e.g. funding of applied safety and security research)
Reducing accidents	++	+++	+
Reducing security incidents	++	+++	+
Enabling early detection of safety and security incidents	+	++	++
Enabling rapid response to safety and security incidents	+	++	+++
Reducing opportunities for malicious misuse of research tools and knowledge	++	+++	+
Increasing information exchange and learning	+	++	+++
Other goals, e.g. cost effectiveness, feasibility, enabling of constructive applications			

Scoring key (qualitative and relative)

++++ Most effective - +++ Relatively effective - ++ Moderately effective - + Somewhat effective

Notes on illustrative framework and scoring: A systemic approach to biorisk management involves assessing how different goals might be most effectively realized by different stakeholders, tools and mechanisms. Mapping of this approach, as the limited table above illustrates, can facilitate planning and assessment both within and among tools and mechanisms. By comparing across rows, each tool can be considered for its effectiveness against different goals. By comparing across columns, the effectiveness of tools and mechanisms for achieving a certain goal can be considered. A comprehensive approach should seek to fulfil all goals in a suite of approaches. It is only through a mutually reinforcing set of tools that countries can reach the most effective level. Examples, including scoring, are illustrative because the most effective tools and mechanisms and their combination will depend on context.

Robust biorisk governance for the responsible use of the life sciences requires awareness of potential risks and threats that may arise, allowing adaptation to the dynamic and evolving science and technology landscape. Surveying the landscape and scanning the horizon for misuse potential and emerging challenges and risks can generate different scenarios for policy options; it can also markedly enhance early detection and offer more flexible and adaptable responses.

The three core pillars of biorisk governance are biosafety, laboratory biosecurity and the oversight of dual-use research ([Section 2.5](#)). Across the world, biosafety has gained more attention than laboratory biosecurity and dual-use research, but all three pillars need better governance. The domains of biosafety, laboratory biosecurity and the oversight of dual-use research are closely related – in theory if not in practice. Approaching these domains collectively under an integrated and comprehensive biorisk management framework has the advantage of recognizing and capitalizing on how the domains are interconnected without minimizing the specific demands, challenges and risks that each presents ([Box 3](#)). Although these domains are closely related, they might be managed differently.

Box 3. A comprehensive biorisk management framework

A global guidance framework for the safe, secure and responsible governance of biorisks should be comprehensive, anticipatory, flexible, enduring and responsive, as outlined below. These features are also relevant for local contexts.

- **Comprehensive:** Given the rapid advances in the life sciences and the convergence of the life sciences with other scientific fields and technologies, governance systems need to address the new risks that are emerging at these interfaces. Thus, a comprehensive framework covers risks stemming from biological agents and toxins, but also extends to risks arising in fields such as synthetic biology, neurosciences, gene drives, bioregulators, genome editing and bioinformatics. Moreover, the convergence of AI with fields such as biotechnology may facilitate AI-enabled cyberattacks. The framework should also incorporate the full spectrum of risks arising from accidents, inadvertent or deliberate misuse that could cause harm to humans, nonhuman animals, plants and agriculture, and the environment. It should include values and principles that guide governance; tools and mechanisms that contribute to the application of values and principles; and input from various stakeholders involved in developing and implementing governance frameworks. A comprehensive framework relies on three core pillars of biorisk governance: biosafety, laboratory biosecurity and the oversight of dual-use research in the life sciences.
- **Anticipatory:** As life sciences rapidly evolve, the governance of biorisks needs to rely on information and the development of tools to identify and anticipate risks, to best prepare current systems to react to unanticipated risks; these tools should be designed and managed by multidisciplinary groups of experts. Foresight approaches offer multiple tools to consider different futures and make explicit assumptions about preferred, probable and possible futures, and provide groups of experts with anticipatory governance options. By integrating diverse and varied perspectives, cognitive biases can be counteracted and blind spots reduced to formulate more robust governance options as well as a more nuanced assessment of risks (*Box 2*).
- **Flexible, enduring and responsive:** The framework needs to be agile to address existing risks, reasonably anticipate emerging risks posed by advances in science and technologies, and exercise appropriate caution for uncertainty and risks. A key element in the good governance of biorisks will be the development of management systems that combine formal mechanisms and top-down measures with informal mechanisms and bottom-up measures. As risks and social context evolve, it will also be important to develop the capacity to regularly assess how distinct goals can be best achieved through different combinations of governance tools and mechanisms and the involvement of various stakeholders, and to adapt approaches and enable innovation in both policies and practices. Building effective biorisk management systems will require experimentation and regular revisiting of tools and mechanisms and their implementation (101-104). It will also require the development of tools and mechanisms to exchange information among different stakeholders.

4.3 Biorisk governance tools and mechanisms for different stakeholders

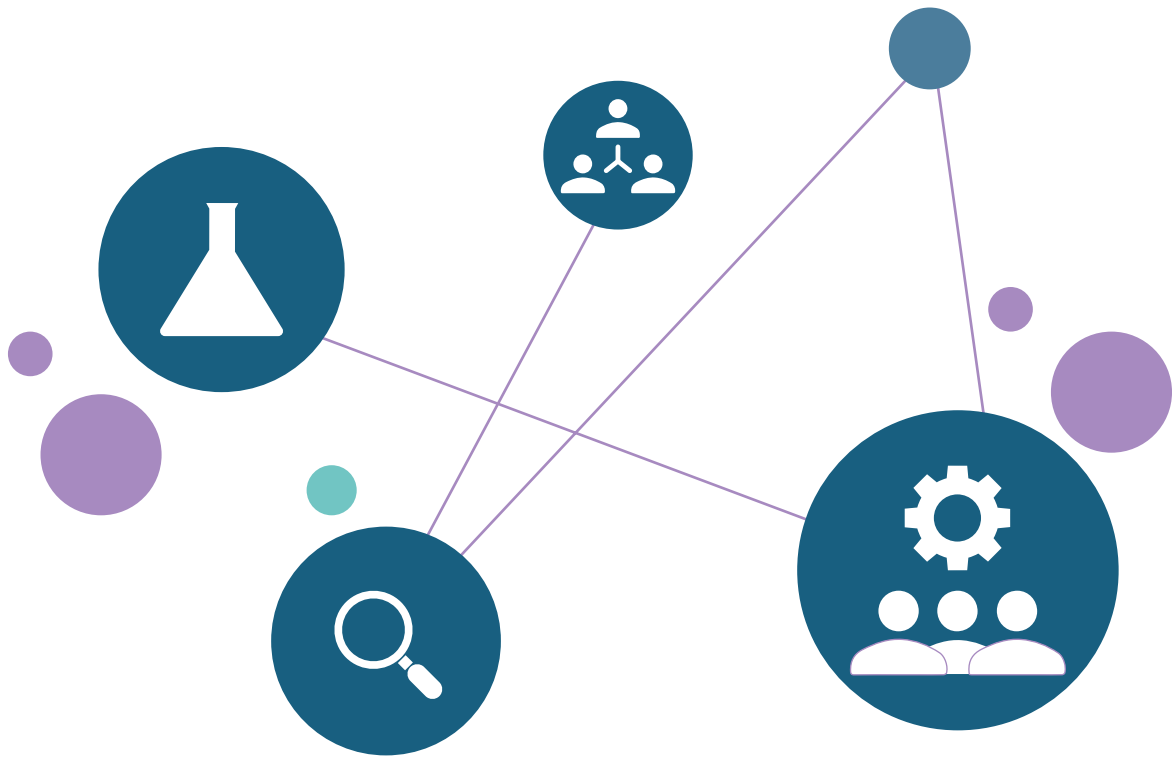
This section outlines examples of biorisk governance tools and mechanisms organized by different stakeholders. Although various stakeholders can work on distinct tools and mechanisms, these will often overlap. For example, research institutions can reduce biorisks with the support of national legislation, regulations and guidelines. The work of scientists can be supported through awareness-raising activities and training developed by academies, institutions, professional organizations and other standard-setting organizations. An important aspect of biorisk governance is that there must be effective and clear communication and collaboration between the various stakeholders. For example, national governments must be able to clearly explain relevant laws and regulations to the appropriate stakeholders. In turn, stakeholders must know and follow their regulatory obligations:



- a. *Scientists* conceive and implement their ideas (although those ideas are clearly shaped by the scientists' environments and communities), and they are the first line of control for assessing, preventing and mitigating risks. Scientists are incentivized to consider, articulate and defend the potential benefits of their work. They also have a responsibility to consider and mitigate any risks that the knowledge, information, methods, products or technologies that they develop and disseminate could be used for harmful purposes.



- b. *Research institutions*, as the employers of scientists, are responsible for their professional activities. Research institutions include all organizations that conduct basic and applied life sciences (e.g. universities, institutes, companies, government laboratories and community laboratories). They are the second line of control for biorisk assessment and mitigation.



c. *National governments* are responsible for enacting and enforcing policies (e.g. laws, regulations, standards, guidelines, best practices, codes of ethics and research review processes). They are ultimately responsible for defining the standards for biorisk management that all stakeholders are required to meet.



d. *Other important stakeholders* include funding bodies, academies, professional societies and other standard-setting institutions, publishers and editors, educators, security actors, international organizations, the private sector, civil society networks, publics, and other venues and networks where biorisks are being addressed. As research is increasingly conducted across different organizations and countries, the roles of various stakeholders in promulgating and translating standards have become more complex and interconnected. For example, in preparing funding proposals and publications, and when implementing projects, stakeholders could consider the possibility of adding information about the risk assessment (e.g. having a paragraph entitled “dual-use research”, to be completed by the authors).

Examples of biorisk management tools and mechanisms for the various stakeholders are illustrated in the following sections.



4.3.1 Stakeholder: National Governments

National governments are key stakeholders that are ultimately responsible for defining the biorisk management standards under their jurisdiction, and for enacting and enforcing relevant policies, including laws, regulations, standards, guidelines, best practices, codes of ethics, research review processes, training and education.

Examples of tools and mechanisms for biorisk management by national governments are as follows:

- a. **Legislation, regulations and guidelines.** These tools can set out legal responsibilities of individuals and institutions for biorisk management, training and internal oversight. However, such frameworks are often drafted in terms of accident prevention and do not necessarily focus on the dual-use nature of scientific advances. Legislation can also help research institutions to understand that their responsibilities to ensure effective biorisk management are not secondary to academic, commercial or other goals.
- b. **Oversight.** A statutory governance system is a tool that can assist with setting minimum national standards, increasing oversight, enabling external audits, encouraging transparency and accountability, and, ultimately, reducing biorisks to an acceptable level. Under such a system, institutions must be registered as suitable to conduct certain types of activities (e.g. genetic modification) or must document biorisk assessment and mitigation when new and particularly risky types of research are proposed.
- c. **Flexible frameworks.** Certain life sciences research is already recognized as particularly risky in some countries (e.g. human genome editing and genetic modification of human pathogens). However, other areas of biorisk are rapidly evolving with advances in technology that are not as clearly defined or governed. For example, in the USA, the Select Agent Regulations provide the legal framework for laboratory biosecurity, and several government-wide policies on dual-use research oversight have been implemented over the past decade (60, 105, 106, 107). However, list-based approaches to governance in the life sciences can be limited. Owing

to the speed of advancements, lists can quickly become outdated, creating gaps in the biorisk management system because new technologies and their associated risks are not listed. Overarching frameworks with sufficient flexibility to apply to new technologies as they arise may avoid this problem. Some countries have adopted a risk-assessment-based regulatory system. For example, in the United Kingdom of Great Britain and Northern Ireland (United Kingdom), the Health and Safety Executive (HSE) requires all organizations involved in genetic manipulation to register with the HSE and seek approval for particular types of research. In their *Compendium of guidance*, it is a legal requirement for all organizations undertaking genetic manipulation to have an internal committee to review the research and risk assessments and can refuse permission to proceed (108). Although many countries have statutory frameworks regulating biosafety, and several have biosecurity-specific legislation, few currently have legislation or regulations focused explicitly on dual-use.

- d. **Advisory bodies and outreach activities.** Several countries use advisory bodies to obtain advice and recommendations on measures to govern biorisks. For example, in France, the National Consultative Council for Biosecurity (CNCB), which was created in 2015, provides recommendations on potential misuse of dual-use research conducted in biology (109). The CNCB also suggests measures to prevent, detect and counter possible threats (109). In the USA, the National Science Advisory Board for Biosecurity (NSABB), which was created in 2004, addresses issues related to biosecurity and dual-use research at the request of the US government (110). The NSABB provides advice, makes recommendations on biosecurity and the oversight of dual-use research, and has published reports covering different aspects of such oversight. In the Netherlands, the Biosecurity Office, which is within the National Institute for Public Health and the Environment (RIVM), is a knowledge and information centre for the government and for institutions in the Netherlands working with high-risk pathogens, knowledge, information and technologies (111). The Biosecurity Office also aims to increase biosecurity awareness, and develops relevant tools and web applications.



4.3.2 Stakeholder: Scientists

As designers and makers of research projects, scientists are critical in the governance of biorisks. However, many scientists are unaware of their individual responsibility for managing the biorisks associated with their research. Some scientists may be aware of their responsibility but lack the knowledge and relationships to fulfil it. This is especially concerning when novel risks arise and roles may be ambiguous, where proactive engagement is necessary.

Examples of tools and mechanisms for biorisk management by scientists are as follows:

- a. **Training.** Biorisk assessment and mitigation are processes that should be familiar to all life scientists. At a minimum, students, trainees and scientists at all levels must know how to assess and document biorisks in a way that is accessible to co-workers and to internal and external auditors. They must also know how to identify and implement technologies, measures or practices to avoid or minimize the impact of biorisks. Training in risk assessment and risk mitigation is essential to help students, trainees and scientists to understand what is expected for effective biorisk management and how to achieve it. For example, the International Federation of Biosafety Associations facilitates training in partnership with national biosafety organizations and provides certification for biosafety and biosecurity professionals (112). Another example is ABSA International –the Association for Biosafety and Biosecurity, which promotes biosafety as a scientific discipline and provides certification for biosafety professionals (113). Critically, training must go beyond competencies to address commitments, especially where risks may require going “beyond compliance” to include proactively monitoring for non-routine biorisks. If a biorisk is identified, scientists’ reporting responsibilities come into play. Training should ensure that these responsibilities are well understood and that there is clarity regarding what to report and to whom. Training should be interdisciplinary, to highlight that it may be helpful to draw on researchers from different disciplines to identify a broader range of risks (especially in convergent areas) or to identify best practices for risk mitigation.
- b. **Codes of ethics.** Codes of ethics can be a useful tool to raise awareness of the need for biorisk management and to provide norm-setting standards. An early example of a national code of conduct for biorisk management is the Biosecurity Code of Conduct in the Netherlands, which was developed by the Royal Netherlands Academy of Arts and Science (KNAW) (114). There have also been initiatives to outline high-level principles that can serve as references in

developing or amending codes of conduct at national or institutional level. The most recent is the Tianjin Biosecurity Guidelines for Codes of Conduct for Scientists (115). Inspired by the Hague Ethical Guidelines that were developed by the Organisation for the Prohibition of Chemical Weapons, the Tianjin Biosecurity Guidelines emerged from foundational work by China and Pakistan, and were developed collaboratively by InterAcademy Partnership (IAP) leaders, Tianjin University's Centre for Biosafety Research and Strategy, and Johns Hopkins University's Center for Health Security, with input from scientists from 20 countries.

- c. **Aligned research agendas.** Supporting research programmes to develop new knowledge, tools and mechanisms that can help to improve biorisk management provides a strategic opportunity to create incentives for scientists to engage in proactive biorisk management. Applied biosafety and biosecurity research programmes can span technological solutions (e.g. new types of biological or physical containment or monitoring strategies), social and behavioural solutions (e.g. innovations in training), and development of innovative policy approaches (e.g. revisions of regulatory frameworks and the supporting science). This work is often most effective when coupled directly with science and technology research programmes in their earliest stages of development. One example is the integrated policy and practices research programme that was supported over a 10-year period by the multi-university US National Science Foundation Synthetic Biology Engineering Research Consortium (SynBERC); it involved both natural and social scientists, and stakeholders in industry and policy (116). Some of the scientists trained in these settings now have research laboratories dedicated to developing technologies to support biosafety and they have become champions for proactive engagement with biorisk management. The International Genetically Engineered Machine (iGEM) competition is a synthetic biology research competition that has engaged more than 50 000 students in over 60 countries (104, 117). It rewards and recognizes not only technological advances but also innovations in safety, security and social responsibility, and it has become a testbed for policy implementation, engaging groups responsible for biorisk management in many countries.
- d. **National legislation, regulations and guidelines.** These tools can be applied to scientists or institutions to ensure that adequate steps are taken to manage biorisks. For example, Canada's comprehensive, nationwide biorisk management system was promulgated in the Human Pathogens and Toxins Act (118), and is overseen by the Centre for Biosecurity in Public Health Agency of Canada (119).



4.3.3 Stakeholder: Research Institutions

Through hosting research and employing scientists, research institutions constitute the second line of control for biorisk assessment and mitigation. Research institutions include all organizations pursuing basic and applied life sciences (e.g. universities, institutes, companies, government laboratories and community laboratories). Without clear guidance from governments and strong communication systems among institutions to share best practices and facilitate innovation and consensus building, research institutions may face ambiguities in their responsibilities for biorisk management.

Examples of tools and mechanisms for biorisk management by research institutions are as follows:

- a. **National legislation and regulation.** Research institutions play a vital role in supporting their employees, as described above. National legislation is a tool that can set out the legal roles and responsibilities of institutions for biorisk management, training and internal oversight. It provides a clear legal framework for measures and activities to ensure that the institutions understand their legal responsibilities for the activities of their employees, and to ensure that biorisk management is not secondary to an institution's academic, commercial or other objectives. The ability of research institutions to undertake research safely, securely and responsibly will vary among Member States. A regulatory system through which institutions are registered as suitable for certain types of activity (e.g. genetic modification) could help institutions to reduce biorisks, by providing for external regulatory audit and providing specific guidance when an institution undertakes or proposes to undertake new types of work.
- b. **Institutional oversight.** Scientists have many demands on their time; thus, even within a robust research culture, there is the possibility of substandard risk assessment and mitigation. Institutional oversight of scientist-led risk assessments (e.g. through internal audits, internal peer review and internal committee approval) can be used to standardize processes within an institution and improve or ensure the quality and timeliness of risk assessments. For example, in Germany, institutions and organizations that receive funding from the German Research Foundation (DFG) are asked to create a committee to review and advise scientists and funders on security-relevant research risks. This advisory process is overseen and supported by the Joint Committee on the Handling of Security-Relevant Research, an advisory committee that aims

to strengthen self-governance of the sciences and humanities regarding security-relevant ethical aspects of research, which also includes biosecurity issues. The committee is run by DFG and the German National Academy of Sciences Leopoldina (120).



4.3.4 Stakeholder: Funding Bodies

Most research institutions are dependent for some of their research funding on external grants, philanthropic funding or contract-awarding bodies.

Examples of tools and mechanisms for biorisk management by funding bodies are given below.

- a. **Research design review.** Although funding bodies are not typically involved in the design of research, they can help to mitigate biorisks through their research application processes. Many leading life sciences funders include questions on their funding application forms to determine whether applicants have considered safety, security and dual-use aspects of their research. These funders also ask peer reviewers to consider biorisk aspects of the proposals they review.
- b. **Funding requirements.** For research that involves potentially high-risk materials, techniques or technologies, funders can make it a condition of funding that scientists proactively identify and manage risks possibly connected with their research; explain how the risks (as managed) are proportionate to the potential benefits of the research; consider whether less risky forms of research could be equally beneficial; and modify the research design, or the dissemination and publication plans (as the research proceeds or after the research has been completed) to mitigate risks. For example, in the United Kingdom, the Biotechnology and Biological Sciences Research Council (BBSRC), the Medical Research Council (MRC) and the Wellcome Trust have conditions for funding that include compliance with risk-related regulations (121). In the European Union (EU), the established Ethics Appraisal Scheme for EU-funded research contains special questions and requirements for projects that involve the risk of misuse (122). The European Commission has issued special guidance to facilitate compliance with international, EU and national laws that address concerns relating to potential misuse of materials, technologies and information. Among others, it asks applicants and researchers to consider appointing an independent ethics adviser or project security officer (or both) or an ethics board or a security advisory board (comprising experts from different backgrounds who, in principle, are not involved in managing the project's research activities) to assist

in designing and implementing the relevant measures for the project. Funders can also raise visibility by requiring disclosures of the process and the presence of risk management throughout the research life cycle (including in publications) to facilitate knowledge sharing and instil norms of managing biorisks. Nascent efforts towards public reporting include the materials design analysis reporting (MDAR) framework (123), developed by a consortium of publishers, which was recently updated to include a question about dual-use, and the Visibility Initiative for Responsible Science (VIRS), developed by an international consortium of funders, publishers, researchers and oversight groups, which aims to develop frameworks to facilitate increased transparency in biorisk management practices through case studies and reporting (124, 125). Funding bodies could also support researchers and institutions by funding personnel who would bring expertise and support to researchers in biorisk management (e.g. administrators being hired to work on data management).

- c. **Agenda setting.** Funding bodies may have a role in setting the research agenda in certain fields. This is an executive function and allows funders to engage with institutions (both individually and collectively) to provide guidance on assessment and control of biorisks, requiring institutions to undertake and maintain certain levels of biorisk assessment, education and training as a condition of eligibility. For example, a consortium of organizations that fund and otherwise support gene drive research – including the Wellcome Trust, Institut Pasteur and Bill & Melinda Gates Foundation – developed a set of guiding principles for sponsoring gene drive research, including promoting safety and governance of the technologies, ensuring transparency in data sharing and fostering accountability (126). Another agenda-setting opportunity is for funding bodies to support lines of research dedicated to developing and evaluating tools and mechanisms to support biorisk management, including both technical and social and behavioural approaches.
- d. **Active accountability.** In the case of known or public examples of scientists or their institutions failing in their duty to identify, assess or control biorisks, funding bodies may consider whether to review extant (and pending) grants. This would be a powerful tool to encourage scientists and institutions to take their responsibilities.



4.3.5 Stakeholder: Publishers and Editors

Particularly in academic fields, publication of research findings is an important component of the research enterprise and has a profound effect on the careers of researchers.

Examples of tools and mechanisms for biorisk management by publishers are as follows:

- a. **Manuscript review.** Review of manuscripts by editors, peers and, in some cases, advisory boards for information that may pose significant biorisks or allow others to inappropriately repeat risky experiments is critical. Although editors and publishers have an obligation to make scientific information (e.g. ideas, knowledge and data) available and accessible, this does not apply when a risk assessment concludes that wide dissemination through publication poses a safety or security threat. In such cases, dissemination may be curtailed. This could mean that manuscripts are not published in full or are significantly modified before publication. The developers of the aforementioned MDAR framework (123) have experimentally included a question related to dual-use in standardized reporting of methods, which must be answered when submitting a paper. Other related initiatives such as VIRS (124) are seeking to develop improved reporting standards throughout the research life cycle.
- b. **Guidelines.** Some publishers have established guidelines for identifying, reviewing and publishing papers that may pose a risk to health, safety and security. These guidelines require periodic revision and updating to ensure inclusion of novel types of potential risks. In 2003, editors from several renowned journals issued a statement on scientific publications and security that included recommendations on editorial processes for publications that may pose a safety or security threat (127). Moreover, in 2006, the Council of Science Editors published a white paper on publication ethics, which has since been updated several times (128). The paper includes a section on the responsibilities of editors towards the public, encompassing guidance on biosafety and biosecurity topics. In the USA, the NSABB has integrated guidance to publishers and editors in several reports on biosecurity, dual-use and gain-of-function research (129).



4.3.6 Stakeholder: standard-setting institutions

Examples of tools and mechanisms for biorisk management by standard-setting institutions are as follows:

- a. **Science academies.** Local and regional science academies, such as the IAP or the European Academy of Sciences and Arts, are important in setting science policies, strategies and ethical considerations that universities and other research organizations can use to develop their own standards of scientific integrity and codes of ethics. For example, in May 2021, the Swiss Academies of Arts and Sciences, together with the Swiss National Science Foundation, the umbrella organization of the Swiss universities, and the Swiss Innovation Agency published a code of conduct for scientific integrity, which includes the following sentence on dual-use research: “Researchers are obliged to proactively recognize and consider possible harms and risks in connection with their research work and to take appropriate precautionary measures. This is especially true for dual-use research of concern” (130).
- b. **Local and regional biosafety associations.** Biosafety and biosecurity officers are key players in assessments of biorisks and implementation of mitigating measures (131). WHO recommends that all laboratories have a biosafety officer to provide advice and guidance to scientists and the laboratory management. For biosafety officers to be competent and capable of supporting their institutions in biorisk management and awareness raising, they need to be sufficiently trained in these matters; they also need to be empowered and trusted members of the research team. Formal and informal peer training can be conducted through local and regional biosafety associations and other entities dedicated to minimizing biorisks (132). The Croatian Society for Biosafety and Biosecurity is a national association that is active in advancing biosafety and biosecurity training and information sharing between biosafety professionals (133). Other examples are found in the Netherlands (111) and Canada (134). Supporting the work of local and regional biosafety associations is key to enhancing biosafety and biosecurity globally.
- c. **International standards.** In 2019, the International Organization for Standardization (ISO) released ISO 35001, a standard for biorisk management for laboratories and other related organizations (63). Rather than focusing on scientific hardware, the standard emphasizes commitments by top management (e.g. to provide adequate resources, to prioritize and communicate biosafety and biosecurity policy, to train staff

and to establish performance expectations). The standard also requires continual improvement of practices and processes to determine the causes of incidents and other issues, to correct problems so that they do not recur, to identify opportunities for improvement, and to recognize and reward improvement. Some institutions have begun adopting the standard, and its further promotion together with awareness-raising efforts will contribute to safer and more secure biological activities. Another example is BioRoboost, an EU-funded project with the goal of fostering standardization in synthetic biology, including standards for increased biosafety and easier risk assessments (135).



4.3.7 Stakeholder: educators

Examples of tools and mechanisms for biorisk management by educators are as follows:

- a. **Introducing responsible science concepts, including biosafety, biosecurity and dual-use.** Integrating concepts pertinent to conducting responsible research into scientific and medical curricula can enhance awareness of risks to health, safety and security in basic and applied life sciences. Academic and scientific institutions can help by including these concepts in their courses and educational activities.
- b. **Training.** Curricula with laboratory and practical sessions can include training sessions that reinforce concepts related to best practices, to apply and reinforce concepts covered in theory sessions. Active learning is effective for demonstrating the practical utility of concepts such as biosafety, biosecurity and dual-use. For example, the Academy of Sciences of Malaysia has developed an educational module for responsible conduct of research in the life sciences that uses active learning principles in a module about dual-use research and the importance of creating a culture of safety (136).



4.3.8 Stakeholder: international organizations

Examples of tools and mechanisms for biorisk management by international organizations are as follows:

- a. **Guidance documents.** Many countries, regions, territories and institutions have developed regulatory frameworks that govern responsible science and offer guidance on related matters; however, others do not have similar tools and mechanisms in place. International organizations (e.g. WHO; FAO; the United Nations Educational, Scientific and Cultural Organization [UNESCO]; and WOAHA) can provide guidance for developing local regulations and also in reinforcing global best practices. For example, WOAHA has published *Guidelines for responsible conduct in veterinary research: identifying, assessing and managing dual use* (137). There are also multilateral efforts to establish metrics related to biorisk management and track countries' performance based on those metrics. For example, UNSCR 1540 (17) includes provisions on biosecurity and the prevention of non-State actors from acquiring and using biological weapons. Another example is the joint external evaluation (JEE) (138), which is a voluntary, collaborative, multisectoral process to comprehensively assess a country's capacity to prevent, detect and rapidly respond to public health risks in the framework of the International Health Regulations (2005). The JEE has been developed and implemented in concordance and collaboration with related efforts such as the Global Health Security Agenda (GHSA) (18) and the WOAHA's performance of veterinary services (PVS) pathway (139). A third example is the framework of the BWC, which provides the normative foundation for international efforts to prevent the misuse of biology and biotechnology. The treaty's Implementation Support Unit provides assistance to countries in joining the treaty and implementing their obligations (140).
- b. **Access to information and resources.** International organizations can facilitate access to information required, for example, for biorisk assessment, training, conducting responsible science, mitigating risk and developing regulations and other relevant activities. These international bodies can also assist local authorities, scientific institutions and investigators to identify resources for complying with responsible science practices. For example, the UN Interregional Crime and Justice Research Institute (UNICRI) has developed a global network of stakeholders invested in biorisk management. UNICRI acts as a clearinghouse to enable stakeholders to share best practices and training materials (141). The UN Office for Disarmament Affairs promotes education and training

on disarmament (142). The annual meetings of States Parties and experts under the BWC bring together governments and nongovernment experts in biorisk management, to share best practices and lessons learned, and to develop new ideas for strengthening global biosecurity (143). The BWC's confidence-building measures – especially those related to Biosafety Level 4 laboratories and biodefense programmes – also provide transparency into national activities in these areas (83). Biodefense research may also face dual-use dilemma in the course of developing defensive measures against biological threats (45).

- c. **Communication.** The identification of novel global threats and growing sources of biorisk can be achieved by transparent communication among countries and among entities. International organizations can foster communication between stakeholders and the publication of data, research or information necessary for identifying such risks. Examples supported by civil society include the Global Biosecurity Dialogue (144) (in particular, its workstream on emerging biological risks) and the Global Health Security Agenda (including its workstream on biosafety and biosecurity) (18).



4.3.9 Stakeholder: civil society networks and publics

Examples of tools and mechanisms for biorisk management by civil society networks are as follows:

- a. **Transparency.** Civil society is a stakeholder in research or laboratory activity insofar as the risks and potential benefits of such activities affect society at large. Hence, civil society networks should have access to information and discussions related to research and laboratory undertakings that may affect various publics. The BioWeapons Prevention Project (145), which has advocated universalization of the BWC and hosted trainings to raise awareness on biological risk management, has been involved in BWC meetings and discussions. For example, the Nuclear Threat Initiative's Global Health Security Index is a metric that measures the level of national biosafety and biosecurity preparedness (146).
- b. **Informing and educating.** Civil society networks are important for informing publics and educating various sectors of society; they can act as a bridge between the scientific community and the public at large.

- c. **Policy-making.** An informed public can make better decisions in support of political strategies and policies that govern scientific activities. Civil society networks can liaise between scientists and the various publics to balance competing interests, such as the desire for unfettered science and the desire for caution and control. For example, following the devastating 2014–2015 Ebola outbreak in west Africa, a partnership between experts and civil society networks resulted in the formation of the Global Emerging Pathogens Treatment Consortium (GET) (147). This consortium played an important role in organizing the African Voices and Leadership conference on Ebola in Dakar, Senegal, in 2014 (148), where deficiencies, including those related to biosecurity, that compounded the outbreak were identified. The consortium was also able to secure commitments from several governments and develop memoranda of understanding with those governments to limit possible threats.



4.3.10 Stakeholder: private sector

Private companies play an increasingly important role in life sciences research and the development of biotechnology. Biotechnology, agricultural biotechnology and pharmaceutical companies conduct research to support the development of commercial products.

Examples of tools and mechanisms for biorisk management by the private sector are as follows:

- a. **Self-governance.** In 2009, a group of leading gene synthesis companies formed the International Gene Synthesis Consortium and adopted a voluntary system for the screening of customers and gene sequence orders. As part of the screening process, orders are compared against a database of nationally and internationally regulated pathogens and toxins, to determine whether any ordered sequence poses a security risk. If the automated screening system detects a close match between an ordered sequence and a regulated agent, the order and the customer are scrutinized manually (149).
- b. **National legislation.** Research, development and use of GMOs is subject to national legislation in many countries; however, such governance is typically limited to considerations related to biosafety and biodiversity. Even in countries that oversee dual-use research, that oversight is often restricted to publicly funded research. Canada's biorisk management system, promulgated in the Human Pathogens and Toxins Act (118) and

overseen by the Centre for Biosecurity in Canada's Public Health Agency, requires any entity, regardless of the source of their funding, to assess the dual-use risks of any research (62, 119).

Looking at alternative business models that can incentivize responsible behaviour may also be a way forward. One way to incentivize industry could be through the use of standard-setting organizations and positive role models; another could be the identification of good practices and corporate social responsibility. Industry stakeholders are becoming increasingly aware of the need to demonstrate responsibility, safety and security in their work. In addition, industry could play a role in supporting universities and higher educational establishments, to bring issues of responsibility into professional development. The increasing role of the private sector in funding research suggests that oversight mechanisms should cover both private and publicly funded research.

Another aspect of governance by the private sector concerns its role in intellectual property management. For example, the private sector can choose to whom to license a patent, can add limitations on use of the licence and can include conditions in materials-transfer agreements.

4.4 Awareness raising, education, training and capacity-building

4.4.1 Examples of awareness raising, education, training and capacity-building

Values and principles provide the ethical foundations for the responsible use of basic and applied life sciences. Tools and mechanisms for biorisk management provide practical grounding for the application of the values and principles. To ensure uptake and use of these foundational elements, awareness raising, education, codes of conduct, ethical reviews, training and capacity-building are required for stakeholders in the research ecosystem (e.g. scientists, research institutions and funders).

Much has already been done in support of awareness raising and engagement in basic and applied science and related fields, including in the chemical field.²⁰ Some illustrative examples are provided in [Annex 3](#). Although some exercises have completed evaluations that demonstrate success, the extent of such activity is sometimes unacknowledged or underacknowledged. Moreover, although some initiatives have proven both successful and sustainable, it is not always clear whether all such initiatives have been effective.

²⁰ See, for example, NASEM (2018) (27), NAS (2011) (150), NASEM (2017) (151) and NRC (2013) (152).

4.4.2 Lessons from past activities

Past efforts to undertake awareness raising, education, training and capacity-building in relation to biorisks provide several general lessons for those seeking to undertake such activities in the future, as shown in Box 4.

Box 4. Lessons from past efforts in awareness raising, education, training and capacity-building

- Purpose.** The purpose of awareness-raising, education, training and capacity-building efforts varies from enabling self-governance to underpinning formal oversight, promoting discussion and other objectives. It is not always clear what is expected of those being “engaged” or “educated”. Moreover, the challenges and gaps in awareness raising and education vary from addressing accidents (biosafety) to preventing deliberate outbreaks of disease (biosecurity). For preventing accidental disease outbreaks, the work needed is largely in implementation of institutional safety procedures, whereas addressing the hostile use of biology requires considerable work to fully enable students, trainees, scientists and others to deal with such concerns.
- Priorities.** Biosecurity and dual-use are not immediate priorities for most of those associated with basic and applied life sciences, and are not necessarily well understood. For those countries grappling with severe health and environmental challenges, it is a demanding task to weigh security threats associated with the life sciences against other concerns.
- Definitions.** The lack of shared terminology (including the meaning of key terms such as biosafety, biosecurity and dual-use) complicates the sharing of best practices.
- Discussion.** Given the uncertainty about what education and training should entail, how it should be done, why it is necessary and who should be involved, education and training to prevent biorisks must be widely promoted and discussed. As no single approach can meet the needs and conditions of all, the strengths, opportunities and challenges of initiatives should be evaluated to assess the tools and mechanisms, and how the necessary capacity-building can be best provided.
- Inclusion.** Past initiatives involved a broad range of stakeholders. As concerns about biorisks extend beyond those working with pathogens, research organizations, funders, laboratory technicians, professional societies, data managers and curators, publishers, editors, ethics committees, institutional or repository managers, civil society networks and regulators have all roles to play – both as teachers and learners.
- Innovation.** The design and creation of awareness-raising and education materials should integrate best practices. Innovative approaches such as active learning and team learning exercises have proven valuable and have enduring value. Moreover, once created, these approaches could be adapted for future training and shared with other teams.
- Integration.** Material on biorisk management could be integrated into existing training courses on laboratory practice, or courses on bioethics or research ethics as part of wider discussions on responsible conduct of research.
- Bottom-up versus top-down.** Some past initiatives have been bottom-up, essentially emerging organically from individual champions, whereas others have been top-down. Both types of support are required, with top-down support being particularly important in institutionalizing initiatives.

- **Localized materials.** Various materials have been developed for awareness raising, education, capacity-building and training. Organizations and countries require material that is appropriate to their circumstances. In general, promoting security can be difficult because what counts as security and to whom it applies depends on context. There is no one-size-fits-all approach, and scenarios need to be tailored to the local context (in terms of content and delivery), made accessible and promulgated. There are insufficient locally appropriate scenarios for LMIC. In addition to scenarios illustrating global biosafety, biosecurity and dual-use challenges, context-specific content should be developed and should consider local risks and challenges.
- **Champions.** The value of champions, including industry and academic leaders, has been emphasized to promote and promulgate materials for promoting biorisk management. Informal and formal networks are important in creating, identifying and fostering individual champions or groups of champions. Cooperating through sustainable, resourced networks is important to capitalize on the growing attention to responsible conduct of research and open science education.
- **Resources.** Although several education-related initiatives have been launched in the past, many have been difficult to sustain, often because of a lack of funding. Both financial and technical support will be required to undertake activities in these areas, to sustain cooperative networks and curate educational materials. This will be particularly important for LMIC with limited resources for effective biorisk management.
- **Enabling measures.** There is uneven awareness of concerns of biorisks and limited training. Awareness raising, education, training and capacity-building will help to address these gaps. Moreover, tools and mechanisms should be developed to respond to concerns, such as by providing channels for whistle-blowers, in tandem with awareness-raising and other measures. This is particularly important in the case of reporting or responding to the suspicions raised by trainees, students, scientists or other relevant stakeholders.
- **Sustainability.** Measures to sustain awareness raising, education, training and capacity-building need to be built into initiatives from the beginning. This will require careful consideration of possible incentives for engagement, including relevant career metrics, which could ensure longevity and bottom-up engagement.



5. Section 5

The framework in action

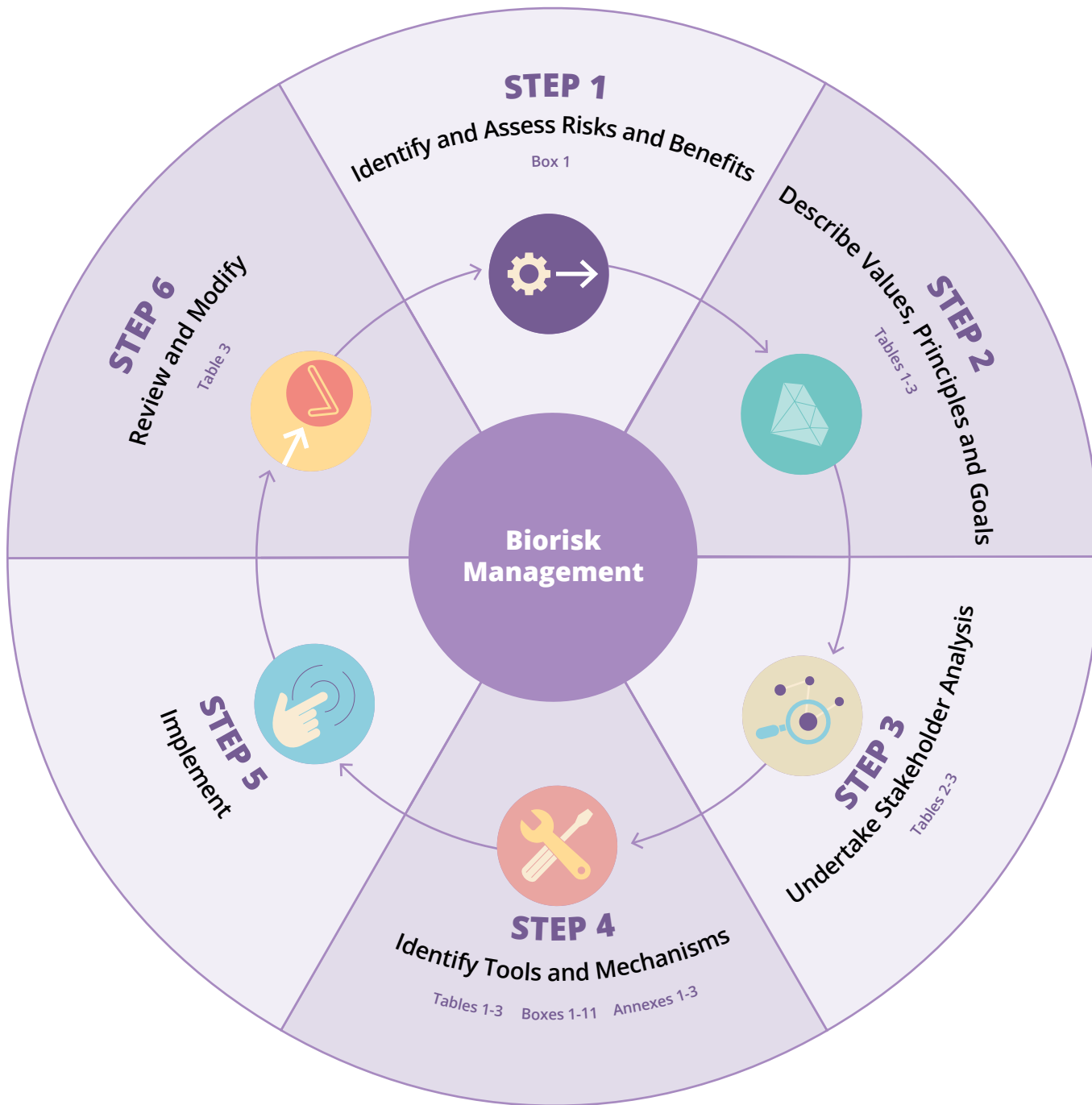
This section outlines how Member States and stakeholders can start implementing the framework and developing biorisk management activities. It is relevant for countries and stakeholders that aim to develop biorisk governance frameworks, and for those interested in strengthening their existing biorisk governance frameworks.

Because there is no one-size-fits-all approach, this section provides checklists of the various steps to be considered for developing a biorisk management framework. The approach is designed for the many different stakeholders involved in the governance of biorisks, and it identifies several key considerations and questions. Each step lists existing resources and tools that can support stakeholders to develop biorisk management activities. For those stakeholders who do not have a checklist in the framework, we encourage you to design your own checklist by using appropriate questions in the existing checklists.

The framework can be operationalized by the implementation of a six-step approach and the checklists. Fig. 1 outlines the generic six-step approach for implementing the framework. Boxes 5–11 illustrate the six steps, with specific checklists applicable to different stakeholders. The checklists are illustrative, but are not exhaustive or prescriptive, and can be adapted as necessary. The checklists help to clarify the minimum expected steps in a complex process; help to anticipate the monitoring and evaluation process by establishing a standard of baseline performance; and provide guidance for countries and other stakeholders who are in the initial stages of reorganizing their biosafety, laboratory biosecurity and dual-use oversight programmes. The checklists will be reviewed and updated in the light of evidence and practices (*Section 1*).

Further guidance and practical toolkits will be developed to assist countries and other stakeholders to adapt and implement the framework.

Figure 1. A stepwise approach for implementing the framework and developing biorisk management activities



5.1 Implementing the framework

Implementation of the framework, using the stepwise approach with the checklists, will be guided by the values and principles and associated commitments for the governance of biorisks (*Table 1*). In addition, implementation will be a process steered by the following key considerations:

- a. **Leadership and ownership:** The process of developing and strengthening biorisk management activities will require leadership and ownership at national and regional levels. Support, guidance, capacity-building and collaboration with key stakeholders will be critical for effective implementation.
- b. **Creating an enabling environment:** Existing expertise and systems can be used and leveraged to facilitate the implementation. For example, existing biosafety systems and procedures can be used as avenues for implementing further biosecurity and dual-use oversight measures. The implementation of the framework and the stepwise approach will need to be adapted to the particular context. Scientists, institutions and countries will start from different points. If there is no legislation, regulations, guidelines or training in place, the stepwise approach can be used to guide discussions and assess the needs of different stakeholders. The stepwise approach could also be used to identify specific national capacities that need to be developed and strengthened. This approach should be evidence based and forward looking.

- c. **Intersectoral collaboration:** The framework encourages dialogue and cooperation among different stakeholders (*Fig. 1, Step 3*). Certain stakeholder groups will be better positioned to achieve specific goals. For example, scientists are best positioned to assess the risks and potential benefits of their work; institutions have an essential role in the oversight of biorisk assessment and mitigation; and governments and regulators are critical in reinforcing and requiring biorisk management strategies across different stakeholders and sectors (e.g. academia, public and governmental laboratories and commercial companies). Different governance strategies, engaging different stakeholder groups, may be taken to achieve a single specific goal.
- d. **Partnership and financing:** Resources and expertise will be required to implement the framework, as will incentives for engaging different stakeholders in the process.
- e. **Monitoring results, measuring success and ensuring accountability:** Biorisk management and mitigation activities should be reviewed regularly. Strategies may need to be adapted in light of new developments. Likewise, effectiveness of mitigation strategies should be assessed and processes for accountability ensured.

5.2 Key considerations for Member States

Depending on the particular country, and its needs and resources, different and complementary pathways can be used to mitigate biorisks and govern dual-use research. Governance measures can include both formal and informal mechanisms:

- a. Examples of laws, regulations and policies associated with the mitigation of biorisks and the governance of dual-use research include those prohibiting certain types of activities (e.g. activities to develop biological weapons); those overseeing the conduct of research with dual-use potential; those controlling the export of certain types of pathogens, research, technologies and information; and those related to the protection of plants, agriculture and the environment ([Section 4.3.1](#)). Several international agreements are relevant to the governance of biorisks and dual-use research; for example, the 1925 Geneva Protocol (11), the 1972 BWC (12), the 1977 Convention on the Prohibition of Military or Any Other Hostile Use of Environmental Modification Techniques (ENMOD) (80), the 1993 CWC (13) and the UNSCR 1540 (17). Different aspects of these international agreements are relevant to the regulation of biorisks and dual-use research ([Section 2](#)).
- b. Guidelines, codes of conduct, and awareness-raising and educational activities pertaining to the responsible use of research and the prevention of misuse constitute another important pathway to implement the framework. There has been much effort in this area ([Section 4.4 and Annex 3](#)) and lessons have been drawn from past experiences ([Box 4](#)).

Depending on the particular country and its resources, there may be options to mitigate biorisks and govern dual-use research through the requirements of biosafety committees, research ethics committees (RECs), national ethics committees and other advisory bodies ([Section 4.3.1](#)).

- a. Biosafety committees are institutional committees created to act as an independent review group for issues related to biosafety; they report to senior management (3). In addition to biosafety and laboratory biosecurity issues, biosafety committees could be one pathway for identifying,

assessing and mitigating potential dual-use risks in the research process (at the proposal or design stage), during the conduct of the research, and at all communication stages (e.g. in manuscripts and conference presentations) ([Section 4.3.3](#)).

- a. RECs review proposed studies related to human or animal experimentation, to ensure that the studies conform to internationally and locally accepted ethical guidelines. They also monitor studies once they have begun and, where relevant, take part in follow-up action and surveillance once the research has ended. Review by a REC is required by international ethical standards governing research involving humans and nonhuman animals, as well as by local law in many jurisdictions.
- b. The main responsibilities of RECs reviewing research involving human participants are to protect the participants and consider the potential risks and benefits to the community in which the research will be carried out. Ethics does not prescribe a specific set of rules or policies; rather, it provides a framework for evaluating problems and determining an appropriate course of action. In bioethics, the most commonly identified principles are individual autonomy (the ability to make decisions for oneself); beneficence (the obligation to “do good” for others); nonmaleficence (the obligation to avoid causing harm to others); and justice (the value of distributing benefits and burdens fairly). These principles provide a general framework for analysis, which can then be applied to the facts of a particular ethical dilemma to reach a resolution (153). As discussed in [Section 2.2](#), dual-use research is often referred to as a dilemma. In this context, and depending on the available structures at country level, RECs could also play a role in overseeing research with dual-use potential.

The checklists given below illustrate some key considerations for national governments to evaluate and discuss existing measures, and measures that could be developed to mitigate biorisks and govern dual-use research. The checklists are not exhaustive or prescriptive, and can be adapted as necessary.

Box 5. Stakeholder: checklist for national governments

Important note: While the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, which is emphasized in STEP 3 of the checklist.

**STEP 1: Collect information****Resources and tools**

Outputs: **National measures for identifying and assessing biorisks and dual-use research potential identified.**

Key considerations include the following:

- Does your country have legislation, regulation or guidelines on laboratory biosafety, biosecurity and the oversight of dual-use research?
 - » What institutional bodies oversee and implement the legislation, regulation or guidelines?
 - » Does your country require risk assessments or risk and benefit analyses of the work done at facilities under your jurisdiction?
 - » Does your country have a system for laboratory licensing?
 - » Does your country have an inventory of pathogens and toxins stored and processed within facilities under your jurisdiction?
 - » Does your country have an inventory of dual-use research conducted in facilities under your jurisdiction?
 - » Does your country have legislation, regulation or guidelines on the transport, sharing and storage of samples?
 - » Do the legislation, regulation or guidelines cover all relevant stakeholders including public and private research institutions, funders, and scientists?
 - » Does your country have plans, and has it exercised those plans, at the regional and sub-regional levels to respond to safety and security incidents at facilities under your jurisdiction?
 - » Is there a system in place to conduct audits in facilities under your jurisdiction?
- Does your country have legislation on export controls?
- Does your country have legislation, regulation or guidelines on the responsible conduct of research that can be relevant to the oversight of dual-use research?
 - » What institutional bodies oversee and implement the legislation, regulation or guidelines?
 - » Do the legislation, regulation or guidelines cover all relevant stakeholders including public and private research institutions, funders, and scientists?
 - » Is there a system in place to conduct audits in facilities under your jurisdiction?
- Does your country provide resources for awareness raising, education and training activities on biorisks, including on dual-use research?

Box 1

WHO JEE tools (P.6.1 and P.6.2) (138)

Global Health Security Agenda action package 3 (18)

Global health security index (146)



STEP 2: Identify the values, principles and goals

Resources and tools

Outputs: **Values, principles, associated commitments and goals are identified.**

Key considerations include the following:

- Ideally, biorisk management would ensure that all values and principles are secured. In practice, however, some situations may cause tension between multiple relevant values and principles that can lead to decisions that prioritize some values and principles (for example, a tension between the values of Health, safety and security and Openness, transparency, honesty and accountability).
- There is no one single approach to resolve potential tensions between different values and principles. This approach will need to take into account local circumstances and contexts. Moreover, decisions on biorisk management should be made using open, transparent, honest and accountable processes. Such processes will help keep making accountable decisions.

Table 1, Table 2 and Table 3



STEP 3: Stakeholder analysis

Resources and tools

Outputs: **All relevant stakeholders involved in and impacted by the management of biorisks are identified and actions are coordinated.**

Key considerations and questions include the following:

- Identify all key stakeholders, and their roles and responsibilities in framing, identifying and managing biorisks (e.g. scientists, research institutions, professional scientific associations, funders, publishers, other governments, publics, the private sector and international organizations).
- Develop a strategy to include key stakeholders in framing, identifying and managing biorisks.
- Describe how you will communicate and coordinate your actions with these actors or groups (i.e. risk communication plan).



STEP 4: Risk management: minimize risks and maximize potential benefits

Resources and tools

Outputs: A set of tools and mechanisms is identified in accordance with the collection of information (STEP1), principles, values and goals (STEP 2)

Key considerations include the following:

- Risk mitigation strategies need to be commensurate with the identified risks.
- Risk mitigation cannot reduce risks to zero unless the work is not undertaken.
- Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms).
- Some tools and mechanisms can be specific to certain goals, whereas others may address several goals at once.
- What measures have been implemented or need to be developed to mitigate the safety, security and dual-use research risks at the national and local levels (Step 1)? Possible questions include the following:
 - » What measures for biosafety, biosecurity and oversight of dual-use research are in place in facilities under your jurisdiction?
 - » What resources and capacity-building support are allocated at research facilities and for personnel to assess and minimize risks under your jurisdiction?
 - » What is the role of institutional bodies such as biosafety committees and ethics review committees in mitigating biorisks?
 - » What training is provided to research institutions and personnel as part of their regular duties to assess and minimize risks?
 - » What systems are in place to share agents, tools, information and samples safely and securely under your jurisdiction?
 - » Is there a surveillance system in place to monitor personnel for potential exposures to pathogens when working in the laboratory or when pathogens are collected in the field?
 - » How is clear communication between the various stakeholders being promoted?
 - » What systems are in place to manage the dissemination of information, to prevent and react to potential misinformation and disinformation?
- Has your country implemented fair processes for the confidential reporting and investigation of possible illegal, unethical or unsafe research or other activities? Do these processes provide appropriate support and protection for both those reporting concerns and those alleged to have engaged in illegal, unethical or unsafe research or other activities?

[Table 2](#) and [Table 3](#)

[Section 4](#)



STEP 5: Implement the identified tools and mechanisms

Resources and tools

Outputs: **The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3).**

Key considerations include the following:

- Consider the feasibility of the set of tools and mechanisms.
- Secure the resources and identify a realistic timeframe.
- Get support from key stakeholders.



STEP 6: Review performance and adaptability

Resources and tools

Outputs: **The approach is reviewed (STEP 1 – STEP 5) and adapted as necessary.**


Key considerations include the following:



- Risk assessment or risk and benefit analyses should be regularly updated.
- Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require that risk mitigation strategies be adapted.
- Effectiveness of mitigation strategies should be assessed.
- Stakeholders should be involved and their feedback sought.

5.3 Key considerations for other stakeholders

Box 6. Checklist for scientists

Note: Although the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, as emphasized in Step 3 of the checklist.

 STEP 1: Collect information	Resources and tools
<p><i>Outputs:</i> Potential risks of work are identified and assessed before beginning the work. If applicable, risk and benefit analyses are conducted before beginning the work.</p> <p>Key considerations and questions include the following:</p> <ul style="list-style-type: none"> - What risks could the proposed work pose to humans, nonhuman animals, plants and agriculture, and the environment? - What are the potential benefits of the proposed work? - Has a risk assessment or a risk and benefit analysis been conducted for the proposed work? <ul style="list-style-type: none"> » How often should this evaluation of the proposed work be reassessed? » Do the benefits of the research outweigh the risks? Should the research be conducted? » Could the information, data and research methods generated by the proposed work be misused to cause harm? What mitigation strategies have been put into place to reduce this risk? - Can a different methodology, experimental design or different organism be used to make the experiment safer or less of a biosecurity risk? - Are safety measures sufficient to protect laboratory personnel and others and the environment from risks? - Are security measures sufficient to protect the material, information, personnel and the environment from undue access? Is the proposed work falling under the scope of export controls? - Does the proposed work follow institutional guidelines, or national or regional legislation, regulations or guidelines for safe, secure and responsible research? 	<p style="text-align: center;"><u>Box 1</u></p> <p>WHO JEE tools (P.6.1 and P.6.2) (138)</p>

 <p>STEP 2: Identify the values, principles and goals</p>	<p>Resources and tools</p>
<p><i>Outputs:</i> Values, principles, associated commitments and goals are identified.</p> <p>Key considerations include the following:</p> <ul style="list-style-type: none"> – Ideally, biorisk management would ensure that all values and principles are secured. In practice, however, some situations may cause tension between multiple relevant values and principles, which can lead to decisions that prioritize some values and principles (e.g. a tension between the values of health, safety and security, and openness, transparency, honesty and accountability). – There is no single approach for resolving potential tensions between different values and principles. The approach chosen will need to take into account local circumstances and contexts. Moreover, decisions on biorisk management should be made using open, transparent, honest and accountable processes. Such processes will help in making accountable decisions. 	<p><i>Table 1, Table 2 and Table 3</i></p>
 <p>STEP 3: Stakeholder analysis</p>	<p>Resources and tools</p>
<p><i>Outputs:</i> All relevant stakeholders involved in and impacted by the management of biorisks are identified and actions are coordinated.</p> <p>Key considerations and questions include the following:</p> <ul style="list-style-type: none"> – Identify all key stakeholders, and their roles and responsibilities in framing, identifying and managing biorisks (e.g. the research institution, professional scientific associations, funders, publishers, government, publics, the private sector and international organizations). – Develop a strategy to include key stakeholders in framing, identifying and managing biorisks. – Describe how you plan to communicate and coordinate your actions with these actors or groups (i.e. risk communication plan). 	



STEP 4: Risk management: minimize risks and maximize potential benefits

Resources and tools

Outputs: A set of tools and mechanisms is identified in accordance with the collection of information (STEP1), principles, values and goals (STEP 2)

Key considerations include the following:

- Risk mitigation strategies need to be commensurate with the identified risks.
- Risk mitigation strategies cannot reduce risks to zero unless the work or research is not undertaken.
- Are there resources to address identified risks?
- Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms).
- Some tools and mechanisms can be specific to certain goals, whereas others may address several goals at once.
- What systems are in place in your institution or at the national level to manage the dissemination of information, to prevent and react to potential misinformation and disinformation?

Table 2 and Table 3

Section 4



STEP 5: Implement the identified tools and mechanisms

Resources and tools

Outputs: The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3).

Key considerations include the following:

- Consider the feasibility of the set of tools and mechanisms.
- Secure the resources and identify a realistic time frame.
- Get support from key stakeholders.

**STEP 6: Review performance and adaptability****Resources
and tools**


Outputs: **The approach is reviewed (STEP 1 – STEP 5) and adapted as necessary.**

Key considerations include the following:

- Risk assessment or risk and benefit analyses should be regularly updated.
- Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require risk mitigation strategies to be adapted.
- Effectiveness of mitigation strategies should be assessed.
- Stakeholders should be involved and their feedback sought.

Box 7. Checklist for research institutions

Note: Although the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, as emphasized in Step 3 of the checklist.

 STEP 1: Collect information	Resources and tools
<p><i>Outputs:</i> Institutional measures for assessing biorisks and dual-use research potential are identified.</p> <p>Questions to consider include the following:</p> <ul style="list-style-type: none"> – What are the purposes of the proposed work to be undertaken at your institution? – What risks could the proposed work pose to humans, nonhuman animals, plants and agriculture, and the environment? – What are the potential benefits of the proposed work to be undertaken at your institution? – Has a risk assessment or a risk and benefit analysis been conducted for the proposed work to be undertaken at your institution? <ul style="list-style-type: none"> » Does the institution agree with the risk assessment or risk and benefit analysis of scientists? » Does the institution agree with the periodicity that scientists have set out for risk reassessment or risk and benefit reassessment? » Do the benefits of the research outweigh the risks? Should the research be conducted? » Could the information, data and research methods generated by this work be misused to cause harm? What mitigation strategies have been put into place to reduce this risk? – Are the personnel and institution qualified to do the proposed work? – Is there a mechanism to determine which personnel are authorized to undertake and access the proposed work? 	<p><i>Box 1</i></p> <p>WHO JEE tools (P.6.1 and P.6.2) (138)</p>

- Is access to sensitive information controlled by adequate policies and procedures?
- Are safety measures sufficient to protect laboratory personnel and others and the environment from risks?
- Are security measures sufficient to protect the material, information, personnel and the environment from undue access?
- Can a different methodology, experimental design or organism be used to make the experiment safer or less of a biosecurity risk?
- Does the proposed work follow institutional, national or regional legislation, regulations or guidelines for safe, secure and responsible research?
- Does the proposed work fall under the scope of export controls?
- Does the institution provide adequate education, training resources, incentives and expertise for the personnel to run safety and security risk assessments, and to increase awareness of risk?

Box 1

WHO JEE tools (P.6.1 and P.6.2) (138)



STEP 2: Identify the values, principles and goals



Resources and tools

Outputs: Values, principles, associated commitments and goals are identified.

Key considerations include the following:

- Ideally, biorisk management would ensure that all values and principles are secured. In practice, however, some situations may cause tension between multiple relevant values and principles, which can lead to decisions that prioritize some values and principles (e.g. a tension between the values of health, safety and security, and openness, transparency, honesty and accountability).
- There is no single approach for resolving potential tensions between different values and principles. The approach chosen will need to take into account local circumstances and contexts. Moreover, decisions on biorisk management should be made using open, transparent, honest and accountable processes. Such processes will help in making accountable decisions.

Table 1, Table 2 and Table 3

 <p>STEP 3: Stakeholder analysis</p>	<p>Resources and tools</p>
<p><i>Outputs:</i> All relevant stakeholders involved in and impacted by the management of biorisks are identified and actions are coordinated.</p> <p>Key considerations and questions include the following:</p> <ul style="list-style-type: none"> – Identify all key stakeholders, and their roles and responsibilities in framing, identifying and managing biorisks (e.g. scientists, other research institutions, professional scientific associations, funders, publishers, government, publics, the private sector and international organizations). – Develop a strategy to include key stakeholders in framing, identifying and managing biorisks. – Describe how you will communicate and coordinate your actions with these actors or groups (i.e. risk communication plan). 	
 <p>STEP 4: Risk management: minimize risks and maximize potential benefits</p>	<p>Resources and tools</p>
<p><i>Outputs:</i> A set of tools and mechanisms is identified in accordance with the collection of information (STEP1), principles, values and goals (STEP 2)</p> <p>Key considerations include the following:</p> <ul style="list-style-type: none"> – Risk mitigation strategies need to be commensurate with the identified risks. – Risk mitigation cannot reduce risks to zero unless the work is not undertaken. – Are there resources to address identified risks? – What training is provided to personnel as part of their regular duties to minimize risks? – Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms). – Some tools and mechanisms can be specific to certain goals, whereas others may address several goals at once. – Does your institution have implemented mechanisms and tools to mitigate safety, security and dual-use research risks? – Does your institution have a biosafety officer or has it established an institutional biosafety and biosecurity committee that will provide oversight of the proposed work? – Does your institution provide education and training about biorisk management to the personnel? 	<p><i>Table 2 and Table 3</i></p> <p><i>Section 4</i></p>

- What systems are in place to report any incidents, accidents and breaches?
- Is there a surveillance system in place to monitor personnel for potential exposures to pathogens when working in the laboratory or when pathogens are collected in the field?
- Has your institution implemented adequate policies and procedures to regulate access to sensitive information (e.g. patient information, customers' confidential data and information with dual-use potential)?
- Has your institution implemented fair processes for the confidential reporting and investigation of possible illegal, unethical or unsafe research or other activities? Do these processes provide appropriate support and protection for both those reporting concerns and those alleged to have engaged in illegal, unethical or unsafe research or other activities?
- What systems are in place to order and share agents, tools, information and samples safely and securely between your institution and other collaborating entities?
- Is there a system in place to conduct audits at your institution?
- What systems are in place in your institution and at the national level to manage the dissemination of information, to prevent and react to potential misinformation and disinformation?

Table 2 and Table 3

Section 4



STEP 5: Implement the identified tools and mechanisms

**Resources
and tools**

Outputs: The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3).

Key considerations include the following:

- Consider the feasibility of the set of tools and mechanisms.
- Secure the resources and identify a realistic time frame.
- Get support from key stakeholders.



STEP 6: Review performance and adaptability

**Resources
and tools**


Outputs: The approach is reviewed (STEP 1 – STEP 5) and adapted as necessary.

Key considerations include the following:

- Risk assessment or risk and benefit analyses should be regularly updated.
- Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require that risk mitigation strategies be adapted.
- Effectiveness of mitigation strategies should be assessed.
- Stakeholders should be involved and their feedback sought.

Box 8. Checklist for funding bodies

Note: Although the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, as emphasized in Step 3 of the checklist.

 STEP 1: Collect information	Resources and tools
<p><i>Outputs:</i> Measures for assessing biorisks and dual-use research potential are identified.</p> <p>Key considerations include the following:</p> <ul style="list-style-type: none"> – What are the purposes of the proposed work? – What risks could the proposed work pose to humans, nonhuman animals, plants and agriculture, and the environment? – What are the potential benefits of the proposed work? – As a funder, does the application for funding include a requirement that grantees assess the proposed work for potential biorisks and consider means of mitigating biorisks? – As a funder, do you have a review process in place to assess the safety, security risks and potential misuse of the proposed work? – Has a risk assessment or a risk and benefit analysis been conducted for the proposed work? If so: <ul style="list-style-type: none"> » Does the funding body agree with the risk assessment or risk and benefit analysis of the scientists? » Does the funding body agree with the periodicity the scientists or institutions have set out for risk reassessment or risk and benefit reassessment? » Do the benefits of the research outweigh the risks? Should the research be conducted? – Can a different methodology, experimental design or organism be used to make the experiment safer or less of a biosecurity risk? – As a funder, can you require that certain biorisk mitigation strategies be implemented for the proposed work throughout its life cycle? <ul style="list-style-type: none"> » What measures are in place to mitigate safety, security and dual-use research risks of the proposed work? Could the information, data and research methods generated by this work be misused to cause harm? Which mitigation strategies have been put into place to reduce this risk? 	<p><i>Box 1</i></p>

- Is there a system in place to conduct audits on the proposed work?
- As a funder, is there a system in place to ensure that researchers who choose not to publish results because of concerns about misuse potential are not disadvantaged with regard to career progression or funding outcomes, and are rewarded for showing responsible scientific practice?
- As a funder, can you require that education and training on biorisk mitigation strategies be provided to grantees?
- As a funder, have you identified any export controls in your country or where the work is being performed?

Box 1



STEP 2: Identify the values, principles and goals

Resources and tools

Outputs: **Values, principles, associated commitments and goals are identified.**

Key considerations include the following:

- Ideally, biorisk management would ensure that all values and principles are secured. In practice, however, some situations may cause tension between multiple relevant values and principles, which can lead to decisions that prioritize some values and principles (e.g. a tension between the values of health, safety and security, and openness, transparency, honesty and accountability).
- There is no single approach for resolving potential tensions between different values and principles. The approach chosen will need to take into account local circumstances and contexts. Moreover, decisions on biorisk management should be made using open, transparent, honest and accountable processes. Such processes will help in making accountable decisions.

Table 1, Table 2 and Table 3



STEP 3: Stakeholder analysis

Resources and tools

Outputs: **All relevant stakeholders involved in and impacted by the management of biorisks are identified and actions are coordinated.**


Key considerations and questions include the following:

- Identify all key stakeholders, and their roles and responsibilities in framing, identifying and managing biorisks (e.g. scientists, research institutions, professional scientific associations, other funding bodies, publishers, governments, publics, the private sector and international organizations).
- Develop a strategy to include key stakeholders in framing, identifying and managing biorisks.
- Describe how you plan to communicate and coordinate your actions with these actors or groups (i.e. risk communication plan).

 <p>STEP 4: Risk management: minimize risks and maximize potential benefits</p>	<p>Resources and tools</p>
<p><i>Outputs:</i> A set of tools and mechanisms is identified in accordance with the collection of information (STEP1), principles, values and goals (STEP 2)</p> <p>Key considerations include the following:</p> <ul style="list-style-type: none"> - Risk mitigation strategies need to be commensurate with the identified risks. - Risk mitigation cannot reduce risks to zero unless the work is not undertaken. - Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms). - Some tools and mechanisms can be specific to certain goals, whereas others may address several goals at once. - What resources for training, capacity-building and educational activities are provided to grantees to assess and minimize biorisks, including dual-use research? - What systems are in place in your institution and at the national level to manage the dissemination of information, to prevent and react to potential misinformation and disinformation? 	<p><i>Table 2 and Table 3</i></p> <p><i>Section 4</i></p>
 <p>STEP 5: Implement the identified tools and mechanisms</p>	<p>Resources and tools</p>
<p><i>Outputs:</i> The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3).</p> <p>Key considerations include the following:</p> <ul style="list-style-type: none"> - Consider the feasibility of the set of tools and mechanisms. - Secure the resources and identify a realistic time frame. - Get support from key stakeholders. 	
 <p>STEP 6: Review performance and adaptability</p>	<p>Resources and tools</p>
<p><i>Outputs:</i> The approach is reviewed (STEP 1 – STEP 5) and adapted as necessary.</p> <p>Key considerations include the following:</p> <ul style="list-style-type: none"> - Risk assessment or risk and benefit analyses should be regularly updated. - Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require that risk mitigation strategies be adapted. - Effectiveness of mitigation strategies should be assessed. - Stakeholders should be involved and their feedback sought. 	

Box 9. Checklist for publishers and editors

Note: Although the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, as emphasized in Step 3 of the checklist.

 STEP 1: Collect information	Resources and tools
<p><i>Outputs:</i> Measures for assessing biorisks and dual-use research potential are identified.</p> <p>Key considerations include the following:</p> <ul style="list-style-type: none"> - What were the objectives of this work? - Who has been funding this work? - What risks could the proposed work pose to humans, nonhuman animals, plants and agriculture, and the environment? - What are the potential benefits and risks of the work? - As a publisher or editor, do you agree with the risk assessment or risk and benefit analysis conducted during the work? - Do the benefits of publishing the research outweigh the risks? - What measures were implemented to mitigate safety, security and dual-use research risks of the proposed work? <ul style="list-style-type: none"> » Were those mitigation measures sufficient to minimize or remove risks identified? - Are there identified government agencies that need to be notified if you identified safety, security and dual-use research risks that were not mitigated during the life cycle of the work being published? - As a publisher or editor, what policy, review process and expertise are in place in your journal to identify manuscripts that contain data, methods and information that could foreseeably be misused by others to cause harm? <ul style="list-style-type: none"> » What actions can your journal take to minimize the risk? - As a publisher or editor, is there a system in place to ensure that researchers who choose not to publish results due to concerns about misuse potential are not disadvantaged with regard to career progression and are rewarded for showing responsible scientific practice? 	<p><i>Box 1</i></p>



STEP 2: Identify the values, principles and goals

Resources and tools

Outputs: **Values, principles, associated commitments and goals are identified.**

Key considerations include the following:

- Ideally, biorisk management would ensure that all values and principles are secured. In practice, however, some situations may cause tension between multiple relevant values and principles, which can lead to decisions that prioritize some values and principles (e.g. a tension between the values of health, safety and security, and openness, transparency, honesty and accountability).
- There is no single approach for resolving potential tensions between different values and principles. The approach chosen will need to take into account local circumstances and contexts. Moreover, decisions on biorisk management should be made using open, transparent, honest and accountable processes. Such processes will help in making accountable decisions.

Table 1, Table 2 and Table 3



STEP 3: Stakeholder analysis

Resources and tools

Outputs: **All relevant stakeholders involved in and impacted by the management of biorisks are identified and actions are coordinated.**

Key considerations and questions include the following:

- Identify all key stakeholders, and their roles and responsibilities in framing, identifying and managing biorisks (e.g. scientists, research institutions, professional scientific associations, funding bodies, other publishers, governments, publics, the private sector and international organizations).
- Develop a strategy to include key stakeholders in framing, identifying and managing biorisks.
- Describe how you plan to communicate and coordinate your actions with these actors or groups (i.e. risk communication plan).



STEP 4: Risk management: minimize risks and maximize potential benefits

Resources and tools

Outputs: A set of tools and mechanisms is identified in accordance with the collection of information (STEP1), principles, values and goals (STEP 2)

Key considerations include the following:

- Risk mitigation strategies need to be commensurate with the identified risks.
- Risk mitigation strategies cannot reduce risks to zero unless the work is not undertaken.
- Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms).
- Some tools and mechanisms can be specific to certain goals, whereas others may address several goals at once.
- In your journal, what resources, training and capacity-building is provided to the journal's editors and manuscript reviewers to be able to flag manuscripts for biorisks, including dual-use research?
- In your journal, what policies and tools are in place to enable the journal's editors to conduct risk assessment or risk and benefit analysis?
- In your journal, what publication strategy (e.g. full publication, delayed publication or publication with accompanying opinion papers) is in place after a comprehensive risk and benefit analysis?
- What systems are in place at your institution and at the national level to manage the dissemination of information, to prevent and react to potential misinformation and disinformation?

Table 2 and Table 3

Section 4



STEP 5: Implement the identified tools and mechanisms

Resources and tools

Outputs: The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3).

Key considerations include the following:

- Consider the feasibility of the set of tools and mechanisms.
- Secure the resources and identify a realistic time frame.
- Get support from key stakeholders.

**STEP 6: Review performance and adaptability****Resources
and tools**


Outputs: **The approach is reviewed (STEP 1 – STEP 5) and adapted as necessary.**

Key considerations include the following:

- Risk assessment or risk and benefit analyses should be regularly updated.
- Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require that risk mitigation strategies be adapted.
- Effectiveness of mitigation strategies should be assessed.
- Stakeholders should be involved and their feedback sought.

Box 10. Checklist for civil society networks and publics

Note: Although the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, which is emphasized in Step 3 of the checklist.

 STEP 1: Collect information	Resources and tools
<p><i>Outputs:</i> Measures for identifying and assessing biorisks and dual-use research potential are identified.</p> <p>Key considerations include the following:</p> <ul style="list-style-type: none"> - Is there publicly available information about the work and potential impacts? - What will be the objectives of this work? - What are the risks and benefits of the work? - What risks could the proposed work pose to humans, nonhuman animals, plants and agriculture, and the environment? <ul style="list-style-type: none"> » What sources of information are available regarding this work or related work that will help to evaluate the risk of this work in an open, transparent, honest and accountable manner? » Is the scientist or the institution where this work will be or is being performed, or another scientific body, available to answer questions about the risks? - Has a risk assessment or a risk and benefit analysis been conducted for the proposed work? - What kind of biorisk mitigation measures have been implemented? - Have other, less risky, methods been considered? - Is there a system in place to conduct audits on the proposed work? - Who will be responsible for responding to potential consequences of the work if it is funded? - Who will be liable for any unintended consequences that may occur? 	<p style="text-align: center;"><i>Box 1</i></p>



STEP 2: Identify the values, principles and goals

Resources and tools

Outputs: **Values, principles, associated commitments and goals are identified.**

Key considerations include the following:

- Ideally, biorisk management would ensure that all values and principles are secured. In practice, however, some situations may cause tension between multiple relevant values and principles, which can lead to decisions that prioritize some values and principles (e.g. a tension between the values of health, safety and security, and openness, transparency, honesty and accountability).
- There is no single approach for resolving potential tensions between different values and principles. The approach chosen will need to take into account local circumstances and contexts. Moreover, decisions on biorisk management should be made using open, transparent, honest and accountable processes. Such processes will help in making accountable decisions.

Table 1, Table 2 and Table 3



STEP 3: Stakeholder analysis

Resources and tools

Outputs: **All relevant stakeholders involved in and impacted by the management of biorisks are identified and actions are coordinated.**

Key considerations and questions include the following:

- Identify all key stakeholders, and their roles and responsibilities in framing, identifying and managing biorisks (e.g. scientists, research institutions, professional scientific associations, funding bodies, publishers, the government or governments, the private sector and international organizations).
- Develop a strategy to include these stakeholders in framing, identifying and managing biorisks.
- Describe how you plan to communicate and coordinate your actions with these actors or groups (i.e. risk communication plan).



STEP 4: Risk management: minimize risks and maximize potential benefits

Resources and tools

Outputs: A set of tools and mechanisms is identified in accordance with the collection of information (STEP1), principles, values and goals (STEP 2)

Key considerations include the following:

- Risk mitigation strategies need to be commensurate with the identified risks.
- Risk mitigation strategies cannot reduce risks to zero unless the work is not undertaken.
- Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms).
- Some tools and mechanisms can be specific to certain goals, whereas others may address several goals at once.
- What resources, education and capacity-building are allocated by governments, funders, institutions and researchers to inform the various publics about the potential benefits and harms of life sciences research?
- What resources and tools are in place for making the various publics aware of the risks and benefits of the life sciences and for empowering them to engage in discussions and decisions about life sciences activities?
- What systems are in place in your organization and at the national level to manage the dissemination of information, to prevent and react to potential misinformation and disinformation?

Table 2 and Table 3

Section 4



STEP 5: Implement the identified tools and mechanisms

Resources and tools

Outputs: The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3).

Key considerations include the following:

- Consider the feasibility of the set of tools and mechanisms.
- Secure the resources and identify a realistic time frame.
- Get support from key stakeholders.

**STEP 6: Review performance and adaptability****Resources
and tools**

Outputs: **The approach is reviewed (STEP 1 – STEP 5) and adapted as necessary.**

Key considerations include the following:

- Risk assessment or risk and benefit analyses should be regularly updated.
- Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require that risk mitigation strategies be adapted.
- Effectiveness of mitigation strategies should be assessed.
- Stakeholders should be involved and their feedback sought.

Box 11. Checklist for the private sector

Note: Although the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, which is emphasized in Step 3 of the checklist.

Within the context of this framework, the private sector is understood as the individuals and organizations that are neither owned nor directly controlled by governments involved in the following:²¹

- a. Research and development (R&D) supporting the development of commercial products. Examples of private sector stakeholders involved in R&D for commercial products include pharmaceutical industries, biotechnology companies, biotechnology incubator facilities and agricultural biotechnology companies.
- b. Provision of research services. Examples of private sector stakeholders associated with the provision of research support services include gene synthesis companies, R&D consultancies and specialized providers of equipment, consumables and maintenance services.

Considerations for private stakeholders have been listed in Box 11. For other stakeholders in the private sector (e.g. private academic or research institutions), other checklists might be more appropriate (e.g. [Box 7](#)). Given that some state-owned organizations are involved in R&D for commercial products and the provision of research support services (e.g. a state-owned contract research organization), the checklist in Box 11 might be more appropriate than the other checklists provided in this framework.

²¹ Adapted from WHO (2020) (154).



STEP 1: Collect information

Resources and tools

Outputs: **Measures for identifying and assessing biorisks and governing dual-use research are identified.**

Key considerations include the following:

- What are the purposes of the proposed work or order?
- What risks could the proposed work or order pose to humans, nonhuman animals, plants and agriculture, and the environment?
- What are the potential benefits of the proposed work or order?
- Is your company and its personnel qualified to undertake the proposed work or order?
- Has a risk assessment or a risk and benefit analysis been conducted for the proposed work or order?
 - » How often should this evaluation of the proposed work or order be reassessed?
 - » Do the benefits of the work outweigh the risks? Should the work or order be conducted or proceed?
- Can a different methodology, experimental design or different organism be used to make the experiment safer or less of a biosecurity risk?
- What measures are in place to mitigate safety, security and dual-use research risks of the proposed work?
- Could the information, data and research methods generated by this work or order be misused to cause harm?
 - » What mitigation strategies have been put into place to reduce this risk?
- Does the proposed work or order follow national or regional legislation or regulations or international guidelines for safe, secure and responsible research?
- Are there any national legislation, regulations or guidelines aimed at overseeing the proposed work or order to reduce the chances of deliberate misuse?
- Is there a system in place to conduct audits on the proposed work or order?
- Does the proposed work or order fall under the scope of export controls?
- Are there identified government agencies that need to be notified if you identify safety, security or dual-use research risks related to the work or order?
- Do the proposed business and the customer meet relevant national legislation and regulations?
 - » Does your company have mechanisms to verify the bona fides of the order or customer?
- Does your company provide access to or funding for educational and training activities on biosafety, biosecurity and dual-use research for your personnel?
- Does your company provide incentives and expertise for the personnel to run safety and security risk assessments and to increase their awareness of risk?
- Does your company provide adequate support to your personnel to identify biorisks, to undertake risk assessments or risk and benefit analyses, and to identify appropriate biorisk mitigation strategies?

[Box 1](#)



STEP 2: Identify the values, principles and goals

Resources and tools

Outputs: **Values, principles, associated commitments and goals are identified.**

Key considerations include the following:

- Ideally, biorisk management would ensure that all values and principles are secured. In practice, however, some situations may cause tension between multiple relevant values and principles, which can lead to decisions that prioritize some values and principles (e.g. a tension between the values of health, safety and security, and openness, transparency, honesty and accountability).
- There is no single approach for resolving potential tensions between different values and principles. The approach chosen will need to take into account local circumstances and contexts. Moreover, decisions on biorisk management should be made using open, transparent, honest and accountable processes. Such processes will help in making accountable decisions.

Table 1, Table 2 and Table 3



STEP 3: Stakeholder analysis

Resources and tools

Outputs: **All relevant stakeholders involved in and impacted by the management of biorisks are identified and actions are coordinated.**

Key considerations and questions include the following:

- Identify all key stakeholders, and their roles and responsibilities in framing, identifying and managing biorisks (e.g. scientists, research institutions, professional scientific associations, funding bodies, publishers, other governments, the private sector and international organizations).
- Develop a strategy to include key stakeholders in framing, identifying and managing biorisks.
- Describe how you plan to communicate and coordinate your actions with these actors or groups (i.e. risk communication plan).



STEP 4: Risk management: minimize risks and maximize potential benefits

Resources and tools

Outputs: **A set of tools and mechanisms is identified in accordance with the collection of information (STEP1), principles, values and goals (STEP 2)**

Key considerations include the following:

- Risk mitigation strategies need to be commensurate with the identified risks.
- Risk mitigation strategies cannot reduce risks to zero unless the work is not undertaken.
- Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms).
- Some tools and mechanisms can be specific to certain goals, whereas others may address several goals at once.
- Does your company have implemented mechanisms and tools to mitigate safety, security and dual-use research risks of the proposed work or order?
- Has your company appointed a biosafety officer or established an institutional biosafety and biosecurity committee that will provide oversight of the proposed work or order?
- Has your company implemented adequate policies and procedures to regulate access to sensitive information (e.g. patient information, customers' confidential data and information with dual-use potential)?
- Does your company provide education and training about biorisk management to the personnel?
- Has your company implemented fair processes for the confidential reporting and investigation of possible illegal, unethical or unsafe research or other activities? Do these processes provide appropriate support and protection for both those reporting concerns and those alleged to have engaged in illegal, unethical or unsafe research or other activities?
- What systems are in place to report any incidents, accidents and breaches?
- Is there a surveillance system in place to monitor personnel for potential exposures to pathogens when working in the laboratory or when these are collected in the field?
- What systems are in place to order and share agents, tools, information and samples safely and securely between your company and other collaborating entities?
- Is there a system in place to conduct audits at your company?
- What systems are in place at your company to manage the dissemination of information, to prevent and react to potential misinformation and disinformation?

Table 2 and Table 3

Section 4



STEP 5: Implement the identified tools and mechanisms

Resources and tools

Outputs: **The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3).**

Key considerations include the following:

- Consider the feasibility of the set of tools and mechanisms.
- Secure the resources and identify a realistic time frame.
- Get support from key stakeholders.



STEP 6: Review performance and adaptability

Resources and tools

Outputs: **The approach is reviewed (STEP 1 – STEP 5) and adapted as necessary.**

Key considerations include the following:

- Risk assessment or risk and benefit analyses should be regularly updated.
- Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require that risk mitigation strategies be adapted.
- Effectiveness of mitigation strategies should be assessed.
- Stakeholders should be involved and their feedback sought.



6. Section 6

Conclusions

Over recent decades, the pace of development and application of the life sciences has accelerated. Although rapid technological change and emerging technologies can offer great opportunities to achieve the UN SDGs and global health, rapid change can also pose risks to our societies, including safety and security risks.

Assessing, mitigating and monitoring the safety and security risks of life sciences research and converging technologies, to ensure that current and scientific advances in the life sciences and converging technologies are used for the betterment of humanity and the biodiversity of our planet, is a complex endeavour.

- First, there is no one-size-fits-all approach for mitigating these risks. Countries and various stakeholders will have different starting points and they will work in different contexts, with different priorities and resources.
- Second, developing and implementing biorisk management activities and policies to address the opportunities and risks brought by these technological changes can be challenging. Countries and relevant stakeholders can find that rapid technological developments may outpace their capacity to respond. This framework is a global guidance document that is intended to be adapted and contextualized so that it can be operationalized effectively. It will be updated to take into account technical and societal developments as well as experiences in biorisk management.
- Third, mitigating these risks involves a broad range of stakeholders. The development and implementation of biorisk management activities involves different actors, including Member States, scientists and their institutions, funding bodies, journals and publishers, governments, security communities, publics, the private sector, international organizations and other relevant stakeholders. Mitigating these risks will require individual and collective actions among different stakeholders and disciplines.

Effective and robust biorisk management systems rely on three core pillars – biosafety, laboratory biosecurity and the oversight of dual-use research – and they require a range of tools and mechanisms to address both existing and unknown risks. This framework provides a common set of values and principles ([Section 3](#)) to guide decision-making, and identifies various tools and mechanisms that could be used in different contexts and applicable to Member States and stakeholders' different starting points ([Section 4](#)). The evolving

and dynamic science and technology context results in a diversification of risks that requires biorisk management systems to be flexible, responsive and proactive in anticipating changes. Foresight approaches can contribute to the responsible use of the life sciences and the developments of biorisk management systems.

Finally, mitigating biorisks is a shared responsibility. Effective and robust biorisk management involves multiple stakeholders (*Section 4* and *Section 5*). Clearly delineating the roles and responsibilities of multiple stakeholders during the research life cycle is critical for successful biorisk management systems (*Section 5* and *Annex 1*). Collaboration among different actors and sectors should be sought and encouraged. We are all concerned with mitigating biorisks. Together, we can contribute to the safe, secure and responsible use of the life sciences so that all populations can truly benefit from the great potential of these technologies.

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Annex 1. Scenarios

Introduction

The seven illustrative scenarios^{22,23} presented in this annex are intended to demonstrate how different elements of the framework can be helpful in successfully working through different types of situations for a variety of stakeholders. The intent is to help different audiences to develop practical and robust strategies to confront a range of plausible futures. The scenarios bring together the different elements of the framework (values and principles, tools and mechanisms, and stakeholders) and test the framework against alternative plausible futures.

The scenarios are hypothetical yet realistic scenarios in which robust biorisk management is needed. Each scenario poses questions from the perspectives of different stakeholders and suggests biorisk management governance gaps that scientists, institutions, countries, funders and journals should address when designing and refining biorisk management governance tools and mechanisms. Each scenario includes a description of the situation, then identifies examples of risks, values and principles; also, each poses questions that specific types of stakeholders should be contemplating.

A robust life science biorisk governance framework will engage countries, institutions, funders, institutional review boards, journals and scientists in a concerted effort to mitigate the biorisks associated with advanced life sciences research and technology development. Stakeholders along the research continuum have roles to play in ensuring a careful assessment of benefits, risks and gaps, and in working together to create appropriate mitigation strategies in line with international norms and guidelines.

²² The scenarios are hypothetical, but they present realistic descriptions of possible situations. Their purpose is to show how the framework might work in a range of plausible future situations, and illustrate the effectiveness and robustness of the framework, by identifying any potential gaps and issues that might challenge it.

²³ Annex 1 draws directly on the report developed by the WHO global guidance framework for biorisk management scenario development working group 5 (unpublished). Scenario 7 was developed as part of the Biosecurity and Health Security Protection (BSP) case studies WHO Global Guidance Framework for the Responsible Use of the Life Sciences (unpublished).

These scenarios highlight various ethical values and principles that serve as the foundation for advanced life sciences research, and embody the framework. In each scenario, there are several areas of concern for biorisk management and points of intervention to mitigate biorisks. Although multiple stakeholders can and should engage in biorisk mitigation strategies throughout the research continuum, each scenario limits its focus to a subset of issues for educational purposes. Key considerations included in the scenarios do not represent a full list of governance options, nor will all suggestions for governance be appropriate for all environments, especially when resources are constrained. However, the scenarios provide concrete examples of scientific research activities and take the reader through ways to identify and address the biosafety, biosecurity and dual-use research risks that can arise.

Scenario 1.

Gene therapy

This scenario underscores the importance of education and training for biorisk management and dual-use research. It also highlights the biorisk management measures that a scientist and an academic or research institution needs to consider to ensure safe and secure research conduct.

Situation for Scenario 1



Scientist A at the “Cure Research Institute” studies treatments for lung cancers and specializes in gene therapy. In their research, Scientist A uses a viral vector (i.e. a genetically modified version of a virus) to transport genetic material that will modify a patient’s disease-carrying gene into a non-disease-carrying version of the gene. Specifically, Scientist A has created a lentivirus-based system to deliver genetically modified elements to cancerous cells in lung tissue. Lentiviruses usually infect blood cells, but Scientist A has created a modified lentivirus that includes two genes from the measles virus. Scientist A has integrated the hemagglutinin and fusion proteins from the measles virus into the lentiviral particle, allowing the viral vector to target cancerous cells in the lung. However, the measles virus hemagglutinin gene produces the protein that immune systems are most likely to recognize and attack following measles vaccination. Therefore, to get this system to work properly, Scientist A had to create mutations in the hemagglutinin gene so that a patient’s immune system would not attack the viral vector after recognizing the measles virus hemagglutinin protein. Without the introduced mutations in the hemagglutinin gene that allowed the viral vector to escape immune system recognition, the gene therapy treatment might not work with patients who had previously been vaccinated against measles. Over the course of their work, Scientist A has identified several mutations that could be introduced to a viable measles virus to allow it to evade immune memory in vaccinated individuals. Scientist A is excited to publish this research and hopes that it will advance the field of lung cancer treatments.

Risks highlighted by Scenario 1 (other risks may also arise)



Biosafety: The integration of a lentiviral vector genome is a biosafety risk to laboratory workers, because lentiviruses can trigger cancer following exposure. Ordinarily, the nature of lentiviruses means that lentiviral vectors cannot be transmitted via aerosols. In this scenario, a new transmission route via aerosols could be created if integrated envelope proteins enable infection of lung epithelial cells.

Dual-use research: The information gained from this work could be misused to generate a measles virus against which available vaccines are not as highly effective as they would normally be. Additionally, the viral system created in this experiment could potentially be used for further experimentation to attempt to create a more transmissible or more lethal measles virus.

Questions for selected stakeholders highlighted by Scenario 1 (other questions and stakeholders may also arise)

Scientist A:

- » Are the laboratory's biosafety measures sufficient to protect laboratory personnel from risks resulting from potential exposure to the lentiviral vectors?
- » Could a different, less dangerous virus be used for the experiment in place of measles?
- » Could the information generated from this research be misused to create a measles virus that evades immunity conferred by measles vaccination?
- » What level of detailed information, data and research methods concerning the types of mutations and the level of immune evasion they confer should be made publicly available in publications following this research?

Biosafety officer at the research institute:

- » Is a biosafety mitigation strategy in place at the institute? Are biosafety measures sufficient to protect laboratory personnel from exposure, including aerosol exposure?

- » Was a risk assessment conducted before approving this research? Could the information emanating from this study be misused by a malicious actor to genetically engineer a measles virus that the vaccine would not protect against?
- » Could a different methodology or experimental design have been used to make the experiment safer or less of a biosecurity risk?

Values and principles highlighted by Scenario 1 (other values and principles may also arise)



Responsible stewardship of science: Responsible stewardship of science requires stakeholders (including scientists, their institutions and funders) to adequately assess risks and benefits of potential research. Biosafety officers and institutional review boards are institutional bodies that commonly provide this oversight. Each of these entities must consider whether the risks of the potential work are greater or less than the potential benefits that may come from the work, identify whether there are less risky methods or forms of research that could be used to answer the question, and whether any further steps can or should be taken to reduce risk. At a minimum, all local, national and international policies and guidelines should be followed; in addition, each stakeholder should continue to innovate and improve best practices to further reduce risk over the life of the research.

Health, safety and security: Biorisk mitigation strategies should be implemented and followed to enable life sciences research to improve human, animal or environmental health, prevent the life sciences from causing harm and promote peace.

Discussion for Scenario 1

Gene therapy is a powerful technology that uses viral vector systems to provide genetic therapeutic material to treat or stop a disease. In this scenario, biosafety, biosecurity and risk mitigation issues should be assessed before starting the research. The scientists working on the project and the biosafety officer should work together to conduct a meaningful risk assessment and create a risk mitigation plan that considers methodologies, protocols and security measures. Both the risk assessment and the mitigation strategies should be reviewed by the institutional review board before any work begins.

There is limited information and guidelines on how to best conduct a comprehensive risk assessment of viral vector systems in human gene therapy. Therefore, it is extremely important to educate scientists and raise awareness about biosafety and biosecurity risks, teach effective methods for conducting

rigorous risk assessments, and share the types of mitigation tools available to reduce biorisks, including the risk that research findings could be later misused.

Responsibilities of the researcher and the biosafety officer should be precise and understood from the start for better biorisk management. Both the researcher and the biosafety officer should work with the institutional review board to ensure adequate oversight. Research oversight should be undertaken periodically, to check on adherence and effectiveness of the risk mitigation strategies. Such oversight also helps to prevent misuse by monitoring the conduct of research.

As more gene therapy products become available, biosafety and biosecurity frameworks, guidance, and training for scientists and other stakeholders (e.g. health workers) will need to be developed because more groups will have access to such tools.

Priority actions, tools and mechanisms highlighted by Scenario 1, for selected stakeholders to consider (other actions, tools and mechanisms, and stakeholders may also arise)

Academic and research institutions and principal investigators (PIs)

- » Ensure that education and training about biorisk management are available for all scientists and laboratory staff, especially PIs and biosafety officers.
- » Ensure that all laboratory research staff have received such training and promote awareness raising among students and trainees on biorisk management.
- » Promote the culture of biorisk management and reduce the risks of dual-use research through education and training for basic and applied life sciences research.
- » Implement tools and mechanisms to consider biosafety challenges in research laboratories; for example, by appointing a biosafety officer and setting up an institutional biosafety and biosecurity committee or institutional review board.
- » Promote a culture of biosafety and biosecurity for basic and applied life sciences, promote the need for a biosafety officer, and establish an institutional biosafety and biosecurity committee for protocol review of gene therapy research studies or other kinds of higher risk research. The biosafety officer should be well trained and should carefully consider

biosafety and biosecurity during the research review process. The officer should ensure that risk mitigation measures are in place before initiating this kind of research. Once the work has started, the biosafety officer should continue to work with the laboratory staff to provide support for and oversight of the work.

Laboratory staff

- » Be aware of the potential for a new transmission route (in this case, via aerosol), and consider this during the risk assessment and in risk mitigation strategies surrounding this experiment. In this scenario, relevant risk mitigation strategies may include guidance for use of personal protective equipment (PPE) for aerosol-generating procedures, equipment to protect against aerosol exposure, or additional PPE (e.g. respirator).
- » Have a standard operating procedure and manual for the laboratory procedures, for risk mitigation in case of accidents, and for use and disposal of PPE.

Scientists

- » Be aware of responsibilities regarding assessing, preventing and mitigating biosafety and biosecurity risks, and potential research misuse of the information generated by their research.
- » With support from their institutions, commit to responsible communication of their research findings to ensure equitable access to the knowledge generated and to minimize risk of misuse.
- » For those from national regulatory bodies, have the appropriate knowledge to conduct adequate risk assessments.

Scenario 2.

Neurobiology

This scenario demonstrates that many different stakeholders should contribute to minimizing risks associated with dual-use research.

Situation for Scenario 2



Scientist B is a PI who has spent years on funded research on a central nervous system (CNS) bioregulator. A person lacking this particular bioregulator will have a debilitating illness. The cause of the loss of this bioregulator probably relates to malfunctions of the immune system, but how this happens is unclear, and the bioregulator clearly has other complex roles. Scientist B and their colleagues are preparing publication of a paper that aims to clarify the neuronal circuits involved in the debilitating disease, and how the bioregulator functions and malfunctions within that circuit. Scientist B hopes that the information in their paper could eventually lead to methods for effective manipulation of the bioregulator and the circuit, to treat people who suffer from the illness. Scientist B is committed to advancing science on the bioregulator to uncover new techniques for improving patient outcomes. They see great potential benefit in this work and has never considered how malicious actors might use this research to do harm. Moreover, Scientist B has submitted all their projects to the university approval processes and never encountered any questions from university leadership or from funders about the dual-use nature of their work.

When presenting this research at a conference, Scientist B is asked by a member of the audience whether someone could use the information about the structure of the bioregulator to create a drug that inhibits the regulator. (If a drug could effectively inhibit the regulator, it could cause a serious debilitating disease for the exposed individuals.) Scientist B finds this question odd, but quickly answers it and moves on. Later in the day, a colleague of Scientist B, Scientist C, approaches them at the conference and comments on the question asked during the presentation. Scientist C, who works on cannabis chemistry, mentions that the question reminded

them of the time when their mentor talked about how earlier work on the structure and function of cannabis was later misused by criminals to make stronger drugs. Scientist B and Scientist C do a quick online search for misuse of neurobiology research. They find several publications discussing potential dual-use applications of neurobiology research. Scientists B and C realize they do not know a lot about potential misuse of their research, or the risks and ethical implications of their work.

Risks highlighted by Scenario 2 (other risks may also arise)



Dual-use research: Cumulative advances in life and associated sciences have enhanced the potential health benefits of neurobiology research. Studying bioregulation of critical neuronal circuits is essential for understanding certain neurological diseases. However, these advances could increase the possibility of misuse. There is a history of misuse in the field of neuroscience.²⁴ The concern in this scenario is the potential use of Scientist B's research by a malicious actor or group to cause harm.

Questions for selected stakeholders highlighted by Scenario 2 (other questions and stakeholders may also arise)

Scientists B and C

- » How could Scientists B and C learn more about the potential risks of their research and keep themselves apprised of the latest developments and best practices that they could incorporate to help to minimize harmful societal implications?

Institution

- » Has Scientist B received an adequate biosecurity education that would have equipped them to recognize and address dual-use concerns?
- » Has the institution provided any incentives to its researchers to ensure that an adequate biorisk assessment is carried out before research proceeds?
- » How can the institution implement biosecurity checks to advise Scientist B of the dangers of malicious misuse of their research and to require them to consider some means of minimizing the dangers?

²⁴ See, for example, Dando (2015) (1).

Professional scientific association

- » What role can the association play to ensure that its members have a firm grasp of the problem of dual-use and the means to deal with it?

Funders

- » Does the funder have a rigorous biosecurity review process in place to assess the dangers and potential misuse of the proposed research?
- » How can the funder require Scientist B and other grantees to consider some means of minimizing biorisks?

Publishers

- » What review process should potential publishers have in place to identify manuscripts that contain data, methods and information that could foreseeably be misused by others to cause harm?
- » What are the measures that journals could take to minimize the risk?

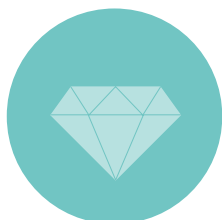
National government

- » Does the country have legislation, regulations or guidelines in place to ensure that biorisks introduced through advanced life sciences research, technology development, and the publication of such research are mitigated or eliminated?
- » Do the governance mechanisms cover relevant stakeholders including public and private research institutions, funders and scientists?
- » How could scientists and risk assessors of national regulatory bodies learn about the potential risks of research and keep apprised of the latest developments and best practices they could incorporate to help minimize harmful societal implications?

International organizations

- » What role can WHO, other agencies in the United Nations system, and nonproliferation treaties such as the Biological and Toxin Weapons Convention (BWC) (2) and the Organisation for the Prohibition of Chemical Weapons (3) play in helping countries, research institutions, professional societies, journals and other stakeholders to minimize risks presented by dual-use research?

Values and principles highlighted by Scenario 2 (other values and principles may also arise)



Responsible stewardship of science: Everyone involved in science has a responsibility to prevent science from causing harm. Part of this responsibility includes educating themselves on the risks, considering how their work fits into the broader society and understanding historical context. At each stage of the research life cycle, various types of stakeholders have an opportunity to intervene to reduce biorisks; responsible stewardship of science requires each stakeholder to try to do this.

Social justice: All entities and individuals in the research enterprise have a responsibility to equitably minimize the burdens of research; this includes considering potential dual-use dangers associated with their work. Understanding how science and research could be misused is a vital component when considering how to balance risks and potential benefits. Consequences of misuse of technology will probably affect vulnerable populations more than others, but benefits of the work might not be accessible to those same populations.

Discussion for Scenario 2

For over 100 years, advances in civil society research in chemistry and biology have been used to facilitate the development of chemical and biological weapons, some of which target the nervous system directly or indirectly. Advances in the life sciences are proceeding at a fast pace, and technologies are becoming cheaper and more accessible. These advances will increasingly determine the types of targets that can be attacked by novel designed agents. This scenario focuses on questions about the impact of these developments generally, not the implications of a single experiment.

Some scientists and international organizations are only now beginning to recognize the dual-use nature of certain kinds of neurobiology research involving the CNS. The International Committee of the Red Cross and various States Parties have led a decades-long campaign to close the possible loophole in the Chemical Weapons Convention (CWC) (4) that could be read as allowing the use of CNS-acting chemicals for law enforcement purposes. In November 2021, the Conference of States Parties to the CWC narrowly took a decision to prohibit such use. Potential misuse of neurosciences has been identified as a concern by some State working papers of the BWC, but much remains to be done in addressing this area of research through improving the relevant tools and governance mechanisms at the individual, institutional, national and international levels.

Priority actions, tools and mechanisms highlighted by Scenario 2, for selected stakeholders to consider (other actions, tools and mechanisms, and stakeholders may also arise)

This scenario underlines the need for improved education and training, so that scientists, institutions, funders, publishers and countries are aware of the problem of dual-use and the potential consequences for broader society. Once these stakeholders understand dual-use, they can apply their expertise to helping to minimize the risk through their daily jobs, both for individual experiments and more broadly in their field.

Scientists

- » Understand how their field of research fits into a broader societal context, which includes considering the risks of the research and historical examples of misuse of the field.

Academic institutions

- » Educate students in science, technology, engineering, arts and mathematics about biorisk management.
- » Incorporate biorisk management ideals and skills into scientific curricula from secondary school biology classes through to doctoral work in basic and applied life sciences, including in biology, biochemistry, bioengineering and other adjacent and relevant convergent fields.
- » Provide continuing education that includes training on dual-use research for all members of the scientific community.

Professional associations

- » Take active roles in educating members about the risks associated with research in the field and the history of misuse or unsafe practices.

National governments

- » Provide resources for education and training on biorisks, including on dual-use research.
- » Develop relevant legislation, regulations and guidelines that include oversight of research with dual-use research potential.

Scenario 3.

DNA Synthesis

This scenario considers how well-intentioned research can be used as the foundation for riskier work, the role of vendors in biorisk management, and how all laboratory members are important in creating a safe and secure environment.

Situation for Scenario 3



Student D is a graduate student in Supervisor E's large laboratory, where the two scientists study host immune response to pox viruses. Student D is specifically focused on understanding the immune response to monkeypox. Supervisor E hopes that this basic science research could eventually help to inform development of a new vaccine. For their first aim, Student D wants to focus on the BR-203 virulence protein, which is believed to help the virus keep the host cell from dying before it can replicate. Supervisor E and Student D decide that the BR-203 gene, which encodes the BR-203 protein, should be inserted into a myxoma virus backbone. Although myxoma has a high lethality for rabbits, it is not known to infect humans and is a close enough relative of the monkeypox virus to be biologically suitable for the experiment. To conduct the research, Student D and Supervisor E have worked with the biosafety officer at their institution, the University of Alias, to determine biosafety protocols for this research.

Student D struggles to get traditional cloning techniques to work for inserting BR-203 into a myxoma backbone. Supervisor E agrees that Student D can order from a de novo DNA synthesis provider the BR-203 gene with part of the myxoma genome on either side. They select a provider that is not a member of the International Gene Synthesis Consortium (IGSC) (5), because it is the cheapest option. Once the order arrives, Student D is able to insert the fragment into the myxoma backbone and conduct their experiments as planned.

Five years later, a new graduate student in Supervisor E's laboratory, Student F, is interested in Student D's previous work. When reviewing Student D's notes, Student F finds the de novo synthesis order information; Student F decides to study monkeypox immune response, but wants to compare host immune responses against monkeypox and myxoma. Student F decides to order the myxoma BR-203 ortholog, M-T4, which has parts of the monkeypox genome on either side of it to make it easier to insert the gene into the laboratory's monkeypox backbone. Student F does not check with Supervisor E before ordering. Student F receives the order and successfully inserts the myxoma virus M-T4 gene into the monkeypox backbone, which was obtained from the laboratory's stock of monkeypox virus. Student F finds Student D's old constructs in the freezer and rescues the old construct to recreate the chimeric viruses that Student D used for their original experiments, to compare immune responses. Once Student F realizes that de novo synthesis can be used to create chimeric viruses, they decide to order more fragments, mixing the genomes together to see at which point the myxoma virus can infect monkeys; to do this, Student F makes use of monkeys that are used in other in vivo experiments in the laboratory and are accessible to Student F. In this way, Student F successfully creates a myxoma virus that is highly infectious for monkeys. Having created a chimeric virus that can infect monkeys, Student F considers infecting themselves with the virus to see whether it can also infect humans.

Risks highlighted by Scenario 3 (other risks may also arise)



Biosafety: Wild type monkeypox virus is infectious to humans whereas myxoma virus is not. Using monkeypox genes to make myxoma virus capable of infecting monkeys creates the prospect that the laboratory experiments will lead to a myxoma virus that can infect humans and make them sick. Technical equipment and PPE protecting laboratory and animal unit staff from infection might not be sufficient with the newly created virus, and might need to be reinforced. A lack of awareness and oversight might lead to situations when laboratory staff are unaware of higher biosafety risks and therefore could unintentionally expose themselves to dangerous pathogens. Infection might be diagnosed too late and spread from laboratory staff to people outside the laboratory. Deliberately infecting oneself with a novel, chimeric virus poses a severe health risk to the researcher, other laboratory staff and members of the community.

Biosecurity and dual-use research: Engineering a virus to give it the ability to infect a new host species is a gain-of-function experiment and an experiment of concern. Several countries (e.g. Australia, Canada and the United States of America [USA]) consider monkeypox virus a potential security risk, and regulate access to this pathogen. In addition, export of the virus is regulated by the Australia Group, an informal forum of 43 countries that harmonize their export controls to prevent the proliferation of chemical and biological weapons (6).

The monkeypox virus genome is also covered by the harmonized screening protocol of the IGSC (5), which was developed by gene synthesis companies. The protocol requires sequence provider members to screen sequence orders and ensure that customers have a legitimate need for the synthetic DNA. According to the IGSC website, 20% of gene synthesis providers around the world are not members of the consortium and are not required by their countries to conduct this screening.

Questions for selected stakeholders highlighted by Scenario 3 (other questions and stakeholders may also arise)

Student D

- » Was a risk assessment carried out before the start of the research work?
- » Should this experiment be conducted or are there safer ways of addressing the research aims?

- » What biosafety and biosecurity information does one need to know to be qualified to do such an experiment in a laboratory?
- » Whose permission is needed to order the DNA fragments?
- » How should materials be stored for future use?
- » Is this work being done safely?
- » Are there biosafety or biosecurity risks associated with this work?
- » What are the future potential consequences of creating chimeric poxviruses?

Supervisor E

- » Should this experiment be conducted or are there safer ways of addressing the research aims? What are the procedures for approving project proposals?
- » Which activities and experiments are undertaken by laboratory staff and students?
- » What biosafety and biosecurity information do students need to know to be qualified to do such experiments in the laboratory?
- » What are the potential consequences of creating chimeric poxviruses? What is the potential for misuse or accidental release caused by this work?
- » Is the work being done safely (e.g. are technical equipment and PPE sufficient and up to date), in line with approved protocols from the institutional review board?
- » Has the risk assessment been done by someone with sufficient expertise (i.e. professional experience or training, or both)?
- » Who has access to materials in the laboratory and can people access materials without the permission or knowledge of Supervisor E?
- » Who can order materials, and can ordering occur without the permission or knowledge of Supervisor E?
- » To whom should Supervisor E report safety and security concerns?

- » Is all research following institutional guidelines as well as local and national guidelines and legislation?

Student F

- » Should this work be done?
- » What biosafety and biosecurity information does one need to know to be qualified to do such an experiment in a laboratory?
- » Whose permission is needed before ordering DNA fragments or reusing old constructs?
- » Whose permission is needed to access monkeypox, a pathogen with a higher biosafety level? What training and qualifications are needed to operate at higher biosafety levels?
- » Are there biosafety or biosecurity risks associated with this work?
- » What are the future potential consequences of creating chimeric poxviruses?
- » What are the risks of infecting oneself with a novel virus? Could this start an outbreak?

Other laboratory members

- » Does the research that Students D and F are working on match what they say they are working on in laboratory meetings or when talking to others?
- » Are all laboratory animals and virus stocks accounted for as expected?
- » If Student F's unauthorized orders of genes, creation of chimeric viruses and experiments with animals and themselves were discovered by another member of the laboratory, would they know who to report this behaviour to and would they be willing to do so?

Biosafety officer of the institution

- » Do the PI and the staff (including students) show a sufficiently high level of biosafety and biosecurity awareness and commitment to following established biosafety and biosecurity guidelines?
- » Have the PI and the staff (including students) received sufficient biosafety and biosecurity training?
- » Have there been biosafety-relevant changes in experiments run in the institution that might change the outcome of risk assessments and even lead to the experiments being classified at higher biosafety levels?
- » As a consequence of changed risk assessments, are the technical equipment and PPE sufficient for the protection of the laboratory staff?
- » Are there rules regulating access to restricted pathogens or laboratories and animal units with higher levels of biosafety? What policies and procedures are in place to ensure compliance with these rules?
- » Are there rules governing who can order potentially dangerous gene sequences?

University of Alias administration

- » Is research being done safely and securely?
- » Is all research following institutional guidelines as well as local and national guidelines and legislation?
- » Has the laboratory worked with the biosafety officer, and has that interaction been sufficient to assess and mitigate risks?
- » Are there rules in place about only allowing staff to place orders with vendors that are members of relevant groups (e.g. IGSC) or that have signed onto a code of conduct?

De novo synthesis company

- » Who is ordering these synthetic DNA fragments?
- » Does the individual and institution ordering the synthetic DNA have a legitimate need and the means to handle safely?
- » Do these fragments pose a biosecurity risk?
- » Could these fragments be misused by the purchaser?
- » What appropriate permissions should be sought before dispatching the order?

Values and principles highlighted by Scenario 3 (other values and principles may also arise)



Responsible stewardship of science: The responsible stewardship of sciences highlights the importance of basic and applied research in the life sciences being conducted in a rigorous and evidence-based manner for the betterment of humans, the planet's biodiversity, ecosystems and environments. In addition, responsible researchers are expected to identify, manage and mitigate reasonably foreseeable potentially harmful consequences of their research through a multidisciplinary review process. Researchers are also expected to exercise caution in the planning and pursuit of their research, and use appropriate biosafety and biosecurity measures to minimize risks to health, safety and security.

Integrity: Researchers are also expected to conduct their work with integrity; this includes conducting their work in accordance with local and national biosafety and biosecurity rules and regulations. Self-experimentation without proper oversight is unsafe and potentially unethical, especially if it creates risks for other individuals. In addition, the results of such an experiment are of limited scientific utility owing to methodological constraints. Finally, researchers are expected to report possible illegal, unethical or unsafe behaviour by their colleagues to relevant institutional, national, regional or international authorities.

Discussion for Scenario 3

In this scenario, the biosafety and biosecurity risks are extreme. There are several potential points of intervention that could have created a safer and more secure laboratory. Student D started their research with good intentions, but a subsequent student misused their work. Supervisor E and the biosafety officer should have had many conversations with Student F before that student got to the point of successfully creating the chimeric viruses, and should have discussed the potential biosecurity and biosafety risks of this work and decided whether to allow the research to take place. Other people working in the laboratory were well positioned to notice inappropriate behaviour or activities from Student F, and if they were properly trained and supported by the institution, they should have been capable of intervening and empowered to do so. The DNA synthesis company should have been screening orders, ensuring that Supervisor E had approved each individual order, and keeping records of what had previously been ordered from that scientist's laboratory.

Supervisor E does not seem to have educated their students sufficiently on biosafety and biosecurity risks, and awareness of these issues is low. For Student F, access to animal experiments, dangerous infectious agents and genetic material has been made too easy, and they have not been sufficiently supervised. There are no access controls for Student F while retrieving Student D's constructs, and there seems to be no requirement for institutional review board approval for this new experimentation. Also, Supervisor E does not seem to keep track of who is working with the more dangerous pathogens in their laboratory, and has not established rules on who has access to monkeypox virus. The institution's biosafety officer should have trained Supervisor E and their students on biosafety issues and raised awareness on these topics. In combination, the lack of awareness and training and the insufficiently regulated access to restricted material has led to a situation where people both inside and outside the laboratory might become infected with a highly pathogenic chimeric virus that could cause an outbreak in the community.

This situation might have been prevented if the gene synthesis company providing the monkeypox genetic material had checked with the institution before filling the order of restricted genetic material, placed by an individual who might not have a legitimate interest in obtaining that genetic material.

Priority actions, tools and mechanisms highlighted by Scenario 3, for selected stakeholders to consider (other actions, tools and mechanisms, and stakeholders may also arise)

This scenario highlights the importance of PIs, students and staff being aware of key biosafety and biosecurity issues; being familiar with the relevant local and national biosafety and biosecurity legislation, regulations and guidelines; and being able to identify biosafety and biosecurity issues relevant to their own work (e.g. critical biosafety aspects of the work done in the laboratory such as transmission routes or host ranges of infectious agents handled, and potential outcomes from genetic modification). To enable this, the PI, students and staff need to be sufficiently educated about biosafety and biosecurity legislation, regulations, guidelines and norms. This education should be provided before the research commences and be updated in regular intervals (e.g. at least once a year).

PI

- » Enable and encourage students and staff to consider biosafety questions themselves and create an open atmosphere, encouraging them to have discussions with the PI.
- » Be a “biorisk management role model” by following general rules such as good microbiology laboratory practice.
- » Keep in contact with students and staff, and be aware of what experiments are running in their laboratory.

Institutions

- » Employ or assign biosafety officers who are responsible for oversight of experiments running in the respective institutions. Ensure that these officers are sufficiently educated on biosafety and biosecurity matters to identify, manage and mitigate research that may pose health, safety or security risks. Biosafety officers should strive to create an open culture that encourages raising awareness and facilitating exchanges on biosafety and biosecurity questions. They should also conduct regular inspections, review and audit of laboratories, with the aim of ensuring that both institutional and national regulations are followed, including controls of stocks of microorganisms.

- » Establish rules governing who has the right to order genetic materials and who has the right to access agents that pose potential health, safety or security risks. The right to order certain materials or access certain stocks of pathogens should be limited to a defined group of people, with a clear process for granting and recording access to these materials.

Gene synthesis providers

- » Follow established protocols for screening of gene sequences and customers. Orders containing regulated pathogens should only be fulfilled if a legitimate interest can be substantiated to the company by the institution ordering it, and if the institution provides evidence of the necessary permits for working with the pathogen. The signature of the PI or an institutional authority might be required for each order of gene sequences coding for select agents or toxins.
- » Gene synthesis companies belonging to the IGSC adhere to a code of conduct that obliges them to perform both gene sequence and customer screening. Oligonucleotides with sequences from an organism on a list of regulated pathogens are only delivered to the customer if additional customer checks are fulfilled. However, not all companies are members of the consortium, creating a gap in biosecurity. National legislation and policies could fill this gap.

National governments

- » Take steps to minimize biorisks of advancing biotechnologies. Risks related to DNA synthesis can be mitigated legislatively through adopting laws, regulations or voluntary guidance that require adequate screening of the sequences ordered and the people placing the order. Box A1.1 describes several biorisk governance measures undertaken in Germany.

Box A1.1. Examples of biorisk governance measures in Germany

It is instructive to look to countries that have governance measures in place to address these types of issues. For example, in Germany, every institution performing genetic engineering operations is required to employ or assign biosafety officers, who need to participate in mandatory training courses. Access to laboratories working with infectious agents (Biosafety Levels 2–4) is restricted to authorized personnel. Laboratory staff working with recombinant organisms must first receive education from the PI on biosafety issues related to the work. PIs themselves are required by law to attend a training course covering risk assessment of genetic engineering operations and related legal requirements before taking up genetic engineering operations. They are personally liable for following national legislation and can be fined for transgressions. Genetic engineering operations with pathogens (as either donor or recipient organisms) need to be authorized by local authorities, who are required to consult a national expert body consisting of honorary experts (the

Central Committee on Biological Safety – ZKBS) on questions of biosafety. Any experiment of Biosafety Level 3 or higher must not start until local authorities have provided official authorization. Experiments are only allowed to be performed in laboratories matching the organism’s biosafety level, and records on any experiment leading to the creation of genetically modified organisms (GMOs) need to be kept by the PI. Local authorities regularly control laboratories and institutions (the frequency depends on the biosafety level) and check biosafety measures, records and stocks.

In other countries, even if not required by law, scientists should be interested and act responsibly in this regard in the interests of the students and staff working in their laboratory. Under European law, there is a legal requirement to regularly update risk assessments of genetic engineering operations.

Scenario 4.

Mutational scanning

This scenario highlights the roles of journals and funders to contribute to mitigating biorisks and the unique positions of private institutions.

Situation for Scenario 4



Researcher G is working at a private company on treatments for infectious diseases. Researcher G is passionate about doing research that could lead to finding better treatments for patients. In particular, they are trying to understand how quickly mutations can arise that allow a pathogen to avoid existing antibodies against the pathogen, which make antibody-based treatments ineffective. To conduct this research, Researcher G does deep mutational scanning (DMS) to evaluate possible point mutations in the pathogen genome and determine which mutations may enable the pathogen to evade antibodies. They make a library of variants of the pathogen and passages those variants with a selection pressure (usually the antibody treatment), to find the variants that continue to replicate despite the presence of the antibody. Following passaging, Researcher G sends the pathogen libraries for genetic sequencing and identifies key mutations, or combinations of mutations, that may contribute to evading antibodies.

Following identification of these mutations, Researcher G sends results to their collaborator, Researcher H, who is a protein engineer based at a government research institution in another country. Researcher H uses Researcher G's DMS data to computationally design new antibodies, which are then synthesized and tested for therapeutic usage. Both researchers wish to publish the unique pipeline and methodology they have created for an emerging pathogen; they write up their results and methods in a manuscript and submit it for publication to a scientific journal. One of the reviewers who received their submission has concerns that the level of information they are sharing could be misused by someone wishing to create a drug that inhibits efficacy of existing broad-spectrum antiviral therapies used to treat patients.

Risks highlighted by Scenario 4 (other risks may also arise)



Biosafety: This scenario presents biosafety risks that stem from creating variants for which existing treatments are not effective. The risk that such variants might be accidentally released is a biosafety risk. The level of risk depends on how transmissible and virulent each variant is and whether effective countermeasures are available.

Biosecurity and dual-use research: There are multiple biosecurity risks. The risks of misuse should be divided into risks stemming from the information generated by this research (and that might be published), from the methods described and from the products created. In terms of the informational risks stemming from this research if published (or the risks if people were to somehow acquire the knowledge it generated), there is the risk that the mutational information can be misused to create variants for which treatment is not yet widely available. Another risk is that the information about which mutations are likely to arise and the antibody treatment that might address them could be misused to create drugs that harm these potential treatments.

The second type of risk stems from the methodology published. This methodology could be misused by malevolent actors to create pathogens that evade existing treatments. If the pipeline created by this research is easy to replicate, it might be misused to create similar pipelines for other pathogens. Finally, the variants created by this research might be misused if malevolent actors were to access them.

All of these risks need to be thoroughly assessed before performing any research, to determine whether they should be a source of concern. If potential dual-use research of concern (DURC) is identified, consideration must be given as to whether the work should go ahead and whether the associated risks can be sufficiently mitigated. This includes consideration of whether publication of the research should go ahead and, if so, what level of detail should be included.

Questions for selected stakeholders highlighted by Scenario 4 (other questions and stakeholders may also arise)

Manuscript reviewer

- » Could the manuscript as written plausibly be used as instructions for how to do harm by a malicious actor?
- » Who should be informed about the risks presented by the paper and how should that be done?

Journal editor

- » How should the journal editor assess the risks of this paper?
- » Are the risks serious enough to merit a special review? How should the journal editor determine that? (How easy or difficult is it to misuse the information in the paper? Are there actors who have shown intentions to misuse such information? Are the benefits large enough to offset the risks?)
- » Who can the journal editor ask to review this paper and assess the potential risk of sharing this information through publication? Who are the experts on such topics (science and biosecurity)?
- » How could the journal editor publish this paper but minimize the potential risk? (Should the publication be delayed while the journal editor puts into place a risk mitigation plan?)
- » Can the journal editor publish the results but only include a vague methodology or redact some of the information?

Private institutions

- » How should private institutions vet collaborations and ensure that appropriate oversight is not slipping through the cracks owing to miscommunication?
- » How should private institutions monitor and react to collaborations when a project begins to show signs of dual-use research potential?

Funders

- » Have funders provided a careful level of oversight to this public–private partnership, to reduce biosafety, biosecurity and dual-use research risks?
- » Was a procedure built into the application for funding to assess the proposal for potential biorisks?
- » Should funders require that certain biorisk mitigation strategies (including biosafety measures) be implemented?

Values and principles highlighted by Scenario 4 (other values and principles may also arise)



Responsible stewardship of science: Journals and publishers, public and private institutions, and funders all have a responsibility to be sound stewards of science. Each entity should actively participate in and promote biorisk management.

Fairness: Journals and publishers, public and private institutions, and funders should have mechanisms built into their processes to ensure fair outcomes from their work. Journals and publishers should have protections in place for reviewers who report biosecurity or dual-use research concerns in a manuscript they are reviewing. Institutions, regardless of whether they are private or public, should have whistle-blower protections and foster an environment that allows staff to question whether work already in progress has become unsafe or a potential biosecurity threat. Staff that raise biosecurity concerns about their work or others' work should not be punished, and such action should be encouraged. Funders should not penalize groups that have previously halted research because of safety or security concerns, or groups that require more money to adequately implement safety and security measures.

Discussion for Scenario 4

Journals and publishers, funders, private institutions and patent agencies are often overlooked in biorisk management discussions, despite having vital roles to play. Funders are uniquely positioned to intervene before a project begins, and publishers before potentially risky information is widely disseminated. Patent offices may also be important; for example, when they examine patent applications from private companies. Data associated with the invention are usually kept confidential until the patent is granted, which involves a full disclosure of the invention.

In some countries, national policies concerning biorisk management may not apply to private institutions or may apply only to work funded by specific funders. In such cases, it is vital that private institutions, other funders and publishers are proactive in reviewing proposals or work for safety and security risks.

Priority actions, tools and mechanisms highlighted by Scenario 4, for selected stakeholders to consider (other actions, tools and mechanisms, and stakeholders may also arise)

Journal editors

- » Take responsibility for what they publish.
- » With the peer reviewers of manuscripts, consider how the article submissions they work with are contributing to broader society, including considering the current and future biorisks that may arise from an article.
- » Identify experts (in-house or external) for reviews and questions as needed.
- » Determine whether a submitted manuscript may need further review.
- » Have clear policies in place that lay out the steps to screen papers for biosecurity risks and a protocol on how to assess them and determine the best approach (e.g. full publication, delayed publication or publication with accompanying opinion papers). The first step for determining whether a paper has biosecurity risks depends on journal editors and reviewers' awareness of biosecurity risks, and their ability to flag them for further assessment. The same applies to the institutions and funders. The process of awareness raising and education is ongoing and complex, but is necessary if the risks of misuse are to be addressed. Further tools are needed to enable journal editors (and the experts they would solicit) to conduct a proper risk-benefit analysis. In other words, after flagging a paper for appearing risky, a comprehensive review should be conducted, following a publication strategy informed by the assessment.

Funders

- » Assess proposals for biorisks and rely on external expert review and advice in this area.
- » Assess how proposed work may be used and any relevant history of the field of study.
- » Identify options to require stronger biorisk mitigation measures.
- » Consider potential biosecurity and dual-use research risks when assessing proposals. Even if the funding agency (or private funder) is unable to conduct a thorough risk assessment itself, it should be capable of noting there may be a concern and should know who to ask for further review.

Public and private research institutions

- » Be aware of all work being done in their facility and collaborations.
- » Help their researchers screen potential collaborators as needed, and consider any additional biosafety or biosecurity risks that may arise from the collaboration. Institutions must ensure that all work is adequately reviewed for biorisks; at least one institution involved in the collaboration should review the risk assessment and risk mitigation strategy.
- » Identify the biorisks associated with research. Institutions should have in-house staff capable of conducting risk assessments with the research team. They should also have a review board that can review the risk assessment and risk mitigation plans for biosafety, biosecurity and dual-use potential, as appropriate.

National governments

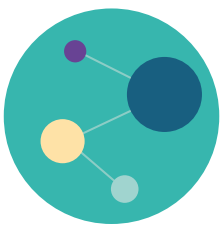
- » Assess possible existing gaps in coverage of biosafety, biosecurity or dual-use research policies. If such policies exist, national legislation should be used to address any gaps. National legislation that applies to all research or work in the life sciences, not just publicly funded research, can strengthen a country's biorisk management framework. When combined with other measures implemented at other stages, such legislation can create a robust biorisk management framework.

Scenario 5.

Mobile public health laboratory

This scenario highlights the biorisks associated with field collection of biological samples, sample transport and public health outbreak response activities.

Situation for Scenario 5



Director Z is setting up several mobile laboratories that could quickly move into an area when an outbreak of an emerging disease occurs. These mobile laboratories will contribute to the creation of diagnostic tests and initial characterization of the pathogen; they will also conduct diagnostic testing and molecular surveillance. Additionally, the staff of these laboratories will help to collect and process environmental and wild animal samples, to assess zoonotic potential and potential spillover events. Part of Director Z's job is developing safety and security protocols for these mobile laboratories and creating training for a pool of people who may be called upon to deploy to these laboratories at short notice. Director Z knows that the people who will be tasked with staffing these laboratories have experience working in diagnostic or research laboratories in their day-to-day jobs; however, Director Z is concerned that the staff may not have experience of working daily with a potentially high-consequence pathogen. Director Z is also concerned that the staff will not be familiar with the potential biosecurity risks associated with working with novel or high-consequence pathogens. Director Z must ensure the mobile laboratories are using appropriate security systems and following all applicable laws, regulations and guidelines for the many different locations where the laboratories will be deployed, and that the mobile laboratories are sending samples to other laboratories in line with export control laws.

Risks highlighted by Scenario 5 (other risks may also arise)



Biosafety: One of the key activities the mobile laboratories in the scenario will participate in is field collection of environmental or animal samples. Such activities often have greater biosafety risks than laboratory-based activities because there are fewer engineering controls available in the field. Staff will have to rely more heavily on PPE and best practices than they would in a research laboratory to maintain a safe environment. Sampling from wild animals in the field is a particularly high-risk activity that will require extensive prior training and biosafety protocols.

Working with novel pathogens or samples of unknown origin may have a higher risk than working in research laboratories (e.g. samples may contain unknown or uncharacterized agents). Similarly, staff may be exposed to an unknown agent in the field. All staff of the mobile laboratories will need extensive training in how to handle samples at higher levels of containment than they may need in their normal working environments. Protocols should include advanced safety measures for samples that may unknowingly contain an infectious agent with altered transmission pathways or a higher risk level than the agent expected to be in the sample.

Biosecurity: Mobile laboratories may be temporarily located in locations with security risks (e.g. civil unrest). Additionally, such laboratories may be targeted by individuals or groups if the situation becomes politicized. The mobile laboratories will need strong security measures to keep staff, samples, equipment, reagents and information safe from potential theft or harm. While people and samples are being transported to the mobile laboratory from the field, or from the mobile laboratory to other facilities in the public health system, they are extremely vulnerable to potential threats. Thus, adequate planning and coordination will be necessary to allow safe and secure transportation.

Information generated from the mobile laboratories will be critical for responding to a public health threat. Protocols for sharing the information must be implemented to ensure the privacy of people in the community, that the correct people receive the information, and that sensitive information is not prematurely released to entities who may wish to misuse or discredit it.

Questions for selected stakeholders highlighted by Scenario 5 (other questions and stakeholders may also arise)

Mobile laboratory director

- » Where can the mobile laboratory director recruit personnel with sufficient biosafety expertise and build a global network of people ready to step in in case of an emergency?
- » What lessons can be learned from outbreaks and outbreak responses in the past?
- » How will information, samples and people be protected and secured in the mobile laboratory, in the field and during transportation?

Public health and health system laboratories and institutions

- » What training should be provided to staff as part of their regular duties in preparation for potential deployment to the mobile laboratory?
- » What capacity do these institutions have to support the mobile laboratory?
- » What systems are in place to share reagents, tools, information and samples safely and securely between these institutions and the mobile laboratory?
- » Is there a national or international standard for safely collecting samples from wild animals and transporting them to the mobile laboratory?
- » How do national or international biosafety standards designed for laboratories in buildings need to be modified for unique challenges posed by the design, construction and operation of mobile laboratories?
- » Is there a protocol in place to ensure secure communication and sample transportation between mobile laboratories and other entities in the public health system?
- » Is there a surveillance system in place to monitor field collection and laboratory staff for potential exposures to pathogens collected in the field or when working in the mobile laboratory?
- » What governmental stakeholders can public health partner with and coordinate with to mitigate security concerns during deployment?

Local, regional and national governments

- » What guidelines are in place to direct the development of safety and security protocols?
- » Who has jurisdiction over the laboratory, and ownership and responsibility for samples, at different times?
- » How should samples be stored, transported and shared?

Values and principles highlighted by Scenario 5 (other values and principles may also arise)



Inclusiveness and collaboration: Processes must be in place to ensure that relevant authorities are consulted before a laboratory is moved into their jurisdiction. Moreover, as information generated by mobile laboratories is likely to be relevant to local, national and international stakeholders, it is important to ensure equitable dissemination of the information to all relevant partners. Because these laboratories are designed to move from one location to another, there must be consideration of the cultural and social context at each location to which the laboratories are moved. Different collection procedures or reporting practices may be needed with different locations; therefore, the organizers of the laboratory must be flexible in implementing changes and adapting protocols, without compromising safety and security.

Discussion for Scenario 5

Research is often the primary activity considered when discussing biorisk management. However, public health, and medical and veterinary clinics and laboratories also conduct work with biological samples that require practitioners to consider biosafety, biosecurity and dual-use potential.

One of the most high-risk activities in the life sciences from a safety perspective is fieldwork, especially with wild animals. There are often many opportunities to unknowingly be infected by an unidentified agent. Similarly, transportation is often one of the most vulnerable stages in a sample's life cycle, being one of the stages where it is hardest to ensure that materials are secured. Such safety and security concerns are amplified in emergency situations, such as during an outbreak.

Priority actions, tools and mechanisms highlighted by Scenario 5, for selected stakeholders to consider (other actions, tools and mechanisms, and stakeholders may also arise)

Mobile laboratory director

Coordinate the development of processes and oversee implementation and training in the mobile laboratories.

Establish an advisory group consisting of individuals from the countries the mobile laboratories may be deployed in, including people who have experience developing mobile laboratories in other countries, members of the public health systems the mobile laboratories will collaborate with, and people with experience and expertise in conducting fieldwork and research with highly pathogenic organisms.

Find personnel to potentially staff the mobile laboratories.

Coordinate with public health and research institutions to find potential personnel who may be called upon to staff the laboratories as needed.

Public health, medical laboratories and other institutions

- » Coordinate with the mobile laboratory director to assess risks and capacity.
- » Use their biorisk management experts and resources to help develop protocols for the mobile laboratories. They may also run protocols and plans through their own review boards to ensure these materials meet standards.
- » Identify how the mobile laboratories will communicate and fit into the larger public health system and consider how this can be done safely, securely and equitably. The public health systems should build their capacity to support biorisk management, both in case the need arises to deploy the mobile laboratories but also in their day-to-day activities.
- » Provide biosafety and biosecurity training to all staff. Additionally, such staff should be made aware of how the expectations may differ between normal activities and emergencies. Special care should be taken to ensure that, even during chaotic emergency situations, protocols are in place to uphold biosafety and biosecurity.

National governments

- » Identify rules in place to govern security of information and samples, especially during transportation.
- » Coordinate with one another and with international agencies to ensure the mobile laboratories are meeting their public health needs while following best practices for safety and security.
- » Have clear guidelines and policies governing how the mobile laboratories should operate in their country, including regarding how to conduct their field collection and laboratory work safely and securely. Rules for hazardous waste disposal and transportation of samples, information and waste should be explicit.
- » Ensure that any existing legislation for biorisk management is written in such a way that public health and medical laboratories, including mobile laboratories, are included in relevant requirements. Guidelines put out by the World Organisation for Animal Health (WOAH) can be a helpful resource to countries in planning for the appropriate and safe deployment of mobile laboratories related to the collection of wild animal samples.

Scenario 6.

Gene drive

This scenario focuses on responsibilities towards public empowerment, environmental stewardship and intergenerational justice, with an emerging technology that has the potential to spread freely in the environment if released.

Situation for Scenario 6



Scientist Y is an ecologist concerned about the expanding range of black rats, an invasive species. Scientist Y is interested in developing a gene drive to control the black rat population, and has designed a gene drive system that would theoretically eliminate 98% of black rats in a given population within 3 years. The modelling of the gene drive and the preliminary studies to assess which genes should be targeted by the drive have been conducted, but the full gene drive cassette has not yet been constructed. After reading an article about the severe problems the black rat is causing in another country, Scientist Y decides to begin planning for their gene drive to be released in that country and to set up a secondary laboratory in that country. Eventually, Scientist Y is ready to create the full gene drive cassette and test it in black rats in a secondary laboratory. Scientist Y is unsure what approvals are needed and from whom before they can conduct this experiment, so they contact the national authority responsible for managing invasive species in the country where their primary laboratory is located. Officials in the agency are unsure of their responsibilities regarding Scientist Y's proposal and are unable to tell the scientist who else they must contact before the gene drive can be tested.

Risks highlighted by Scenario 6 (other risks may also arise)



Biosafety: Appropriate biosafety and animal husbandry measures must be in place for experiments in animals or insects, because this work is often higher risk than cell culture work. Such measures are especially critical if field testing begins, because the field test is a less controlled environment than the laboratory.

Biosecurity: If a gene drive is eventually released, depending on its design, it may be able to self-propagate through the environment. The impacts on the host species, ecosystem and environment may not be predictable and could be severe. Such impacts may last for several generations. Additionally, it will be difficult, if not impossible, to control how far such a gene drive spreads in the wild or to stop it once it has been released. Recalling a gene drive after release is unlikely to be effective. There is significant uncertainty related to potential consequences and the severity of such consequences for gene drives and similar technologies.

Questions for selected stakeholders highlighted by Scenario 6 (other questions and stakeholders may also arise)

Scientist Y

- » How are the risks of the gene drive most appropriately assessed? For example, are there species in the same habitat that might cross with the gene drive rat, possibly creating unintentional spreading of the gene drive? Are there ecological webs in which the black rat may have a role?
- » Is the region intended for the intentional release suitable? For example, a region with a limited exchange between different populations (e.g. a small island) would be desirable to limit the spread of recombinant animals.
- » Is the gene drive stable and, if not, what is the effect on possible offspring?
- » How are genetically modified rats in the laboratory prevented from escaping?

Governments

- » How are the risks of the gene drive most appropriately assessed?
- » What regulations or guidelines are needed to ensure that the work is done safely and securely – both in the laboratory (controlled environment) and eventually at any release sites?
- » Are export controls needed on the technology?
- » What agreements are needed between the government of the researchers, the government of the country where the gene drive will be released, and governments of other countries that may be impacted?
- » Have the local competent authorities concerning this application – such as, a biosafety authority under the Cartagena Protocol on Biosafety (CPB) (7) to the Convention on Biological Diversity (CBD) (8) – been appropriately notified or has a permit been requested?

Publics

- » Is there publicly available information about the research and potential impacts?
- » Are there options for members of various publics to voice concerns, debate and potentially decide whether to release the gene drive?
- » What safety and security reassurances are in place to minimize risk of accidental release during research?
- » Who will be responsible for responding to potential consequences of the gene drive once it is released and funding any required remediation?
- » Who is liable for any unintentional consequences that may occur?
- » Have other, less risky, methods to control this invasive species been attempted?
- » How could release of this gene drive affect indigenous populations and have they been consulted?

Values and principles highlighted by Scenario 6 (other values and principles may also arise)



Intergenerational justice: When considering technologies that could alter ecosystems, intergenerational justice is particularly important to consider as part of assessing risks and conducting work. The health, safety and security of humans, nonhuman animals, plants and agriculture, and the environment for future generations is of particular concern with these technologies that have extensive unknown risks towards the environment and ecology.

Public empowerment: Publics are stakeholders in all life sciences research. However, as gene drives and related technologies have vast potential to spread in the wild rather than being contained to a single facility, publics are critical stakeholders in such work. It is the responsibility of scientists, funders, institutions and countries to ensure that publics are empowered to respond to such work. Furthermore, scientists, funders, regulators and institutions have the responsibility to educate publics about the potential benefits and harms, limitations and capabilities of all basic and applied life sciences, especially for self-propagating genetically engineered agents, in ways that balance competing influences and demands. All involved must exhibit respect for communities, including indigenous populations.

Discussion for Scenario 6

Gene drives and other technologies that are designed to have self-sustained spread in a population are of particular concern to publics and environmental health, both now and in the future. Because such technologies are relatively new, there are significant unknowns related to potential consequences of such technologies if they are released into the wild.²⁵ Owing to the potential environmental and ecological impacts in the near or far term, special attention must be paid to conducting such work safely and securely. The CPB to the CBD includes provisions for the safe transfer, handling and use of living modified organisms (LMOs),²⁶ as well as information required for the risk assessment of these LMOs. These provisions apply to gene drive organisms. However, not all countries are signatories to the Convention or Protocol, creating substantial gaps in oversight for gene drives and similar technologies in those countries. Given that a gene drive could spread across national borders, the lack of policies and oversight in some countries is a risk to all countries.

²⁵ See also the Safe Genes programme of the Defense Advanced Research Projects Agency (DARPA) of the USA, which is developing ways to control, counter and even reverse the effects of genome editing – including gene drives – and to establish “safety by design” (9).

²⁶ LMO means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology. Article 3(g), Cartagena Protocol on Biosafety (7).

A public online registry for gene drive projects has also been proposed and could facilitate oversight and public transparency (10).

Priority actions, tools and mechanisms highlighted by Scenario 6, for selected stakeholders to consider (other actions, tools and mechanisms, and stakeholders may also arise)

Scientists

- » Carefully assess risks and harms. They should consider the real needs and the social value of the research proposed and the environmental impact, and should develop a cautious way of proceeding (firstly in the laboratory, then through the release of rats in controlled habitats, etc.).
- » Consider whether there are alternative technologies or approaches that could have a lower level of risk or uncertainty, before committing to the development of a product through a specific technology.
- » Undertake a community consultation and provide clear information to members of publics.
- » Inform the local government and seek adequate authorizations early in the process (e.g. before setting up the satellite laboratory).
- » Be educated in biosafety and biosecurity and ecological impact on the ecosystem.

Governments

- » Establish oversight mechanisms, with regular checks.
- » Monitor and consider what assurances the researcher and funding agency or institution have, and what mechanisms are available to ensure there is funding for remediation or to deal with possible problems.
- » As a governance pathway, consider regulations concerning GMOs. Such regulations would cover an organism carrying a gene drive; however, gene drives have risks that other GMOs do not have. National legislation should include specific provisions for gene drives and similar technologies. Other national policy and oversight mechanisms could be developed for the governance of gene drives.

- » Have an oversight system (linked to a global framework such as the CPB to the CBD). Depending on how well a country has regulated the field of GMOs and whether it has ratified the CPB, information on applicable regulations (including transboundary movements of GMOs) can be accessed via the country's profile in the biosafety clearing house (11), which is an online platform for exchanging information on LMOs and a tool for facilitating the implementation of the CPB. Countries that are not signatories to the CPB could consider implementing their own registry and regulations to govern such technologies.
- » Conduct a thorough and respectful community consultation and engagement before any release of the gene drive. Communities should be consulted and community authorizations should be secured before any field trials or full releases of gene drives, and appropriate regulatory and ethical approvals should be sought (10).
- » Exercise caution when using procedures that are not accepted in more regulated and controlled countries, in others where such controls are weak or inexistent. Agreements and a system of oversight should be in place before proceeding with this kind of research. It is the responsibility and liability of the researcher, funding agencies and institutions developing these procedures, and this should be clear from the start.

Institutions and funding agencies

- » Require education and training of all scientists involved in gene drive research covering potential ecological risks.

Scenario 7.

International collaboration on high-consequence pathogens research

This scenario underscores issues associated with research on high-consequence pathogens and international collaboration among countries that do not have the same policies on biorisk management.

Situation for Scenario 7



Two research teams, Team W and Team X, are interested in studying the evolutionary potential of a recently emerged subtype of influenza virus. The research the teams are interested in conducting is considered DURC because it could result in the creation of a more transmissible, virulent, infectious or pathogenic strain of influenza. Team W is based in Country A, where there are DURC guidelines that require a risk assessment in advance of the research, and strict monitoring and reporting requirements about the experiments. Team X is based in Country B, where there are few rules specifically aimed at reducing biorisks associated with dual-use life sciences research.

Team W and Team X decide to collaborate on research studying the evolution of influenza. Team W has viral stocks and experience in conducting similar research on other viruses that are not covered by their country's DURC policies (i.e. by Country A's policies). Team X has worked with other subtypes of influenza in the past, but only to study the immune response to the virus.

Together, the two teams develop a strategy to study potential evolutionary pathways of the viruses. The planned experiments include passaging the virus in different environments to understand the impacts of different selection pressures; genetically modifying stock viruses with mutations that increase or decrease transmissibility or pathogenicity in other influenza subtypes; and infecting animal models with the different viruses created via passaging or direct genetic modification, to assess differences in pathogenicity and transmissibility in vivo.

Team W conducts the in vitro work in their laboratory in Country A, which has fewer reporting requirements than are required for in vivo work under Country A's DURC guidelines. Once Team W has generated the mutated viruses, they send those viruses to Team X in Country B. There, Team X conducts the in vivo studies in their laboratory without needing to report any specifics of the research to the authorities in Country B.

Over the course of their work, the collaborating researchers find that they have created new strains of influenza that are more pathogenic than the original strain. They characterize the enhanced pathology and improved fitness of these strains in the Team X laboratory. When the research teams attempt to publish their findings in a top-tier journal, they are surprised to receive an email from the journal editor saying their research has been flagged as a biosecurity concern that will require extra review.

Risks highlighted by Scenario 7 (other risks may also arise)



Biosafety: Recently emerged influenza strains are often considered high-consequence pathogens because of the potential for influenza to jump between species, high transmissibility and differing levels of pathogenicity. The host range of newly emerged pathogens may be unknown, so extra precautions must be taken to minimize the risk of the agent accidentally infecting a wild animal or instigating an outbreak in humans via a laboratory source.

Biosecurity: Transporting samples of infectious diseases, especially across national borders, can increase the risk of theft. Export control regulations must be followed. In the course of their work, the teams have created new strains of influenza that are more pathogenic than the strains occurring in the wild. Neither Country A nor Country B is aware of these developments.

Dual-use research: Information learned during studies evaluating the evolution of viruses may include information that could be misused to genetically engineer a strain of virus that can evade existing therapeutic or prophylactic

agents. Differences in regulations between the two countries could lead to confusion and gaps in oversight. In this case, the governments of both Country A and Country B may be unaware of the work being conducted by the collaborators once the samples are in Country B.

Questions for selected stakeholders highlighted by Scenario 7 (other questions and stakeholders may also arise)

Members of Team W and Team X

- » What are the potential benefits of this research and what are the risks?
- » Was a risk assessment done and do the benefits outweigh the risks?
- » What changes could the experiments cause in the virus? How will the teams monitor these changes?
- » What will the teams do if they identify new strains that are more transmissible, virulent, pathogenic or infectious?
- » To whom should the teams report the creation of a more transmissible, virulent, pathogenic or infectious agent?
- » Is it ethical to look for a location with fewer guidelines to conduct DURC?
- » Are all team members sufficiently trained to conduct the research safely?

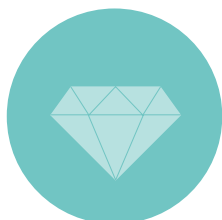
Institutions

- » Is the research conducted at this institution and by the staff of this institution being done ethically and in accordance with any relevant international, national or local governance measures?

Countries A and B

- » What research is being done in this country?
- » Are there gaps in oversight of biological research in this country?
- » Is potentially dangerous research being exported to other countries with different rules for oversight?

Values and principles highlighted by Scenario 7 (other values and principles may also arise)



Responsible stewardship of science: Life sciences research should be undertaken with appropriate biosafety and biosecurity measures, to promote health and the betterment of humans, nonhuman animals, biodiversity, ecosystems and environments. Before work with agents that could pose a threat to any of the entities above is started, it is imperative that risks associated with the work and any mitigation strategies be identified and assessed, to determine whether the risks are proportionate to the potential benefits.

Inclusiveness and collaboration: Risk assessments and appropriate biosafety and biosecurity practices should be adopted, regardless of the country where work is occurring. Thus, the same biosafety and biosecurity practices that are used in Country A should be applied in Country B if the risk of the work being done in both countries is equivalent. The phase of work being completed in Country B is the *in vivo* phase, and animal work typically has higher risks associated with it than cell culture work. Team W and Team X should be increasing or strengthening their biosafety and biosecurity protocols for the phase of work in Country B, even if Country B does not require such efforts to be made.

Discussion for Scenario 7

Research with infectious diseases, especially high-consequence infectious diseases, is vital for preparedness and response to public health threats. However, care must be taken to conduct the research responsibly and minimize the potential for harm. One area of great concern is the potential to generate new strains or variants of a pathogen in the laboratory that is more transmissible, virulent, infectious or pathogenic than strains or variants occurring naturally. Even routine experiments can generate altered strains, variants or viral populations. Although most of the new strains, variants or populations will have little, if any, quantifiable changes from the original sample, there is the potential that the new samples could exhibit a higher risk to human, animal or environmental health. Researchers must be cognizant of the potential changes their experiments could be causing, and adequately address the risks their experiments may pose in their risk assessments.

In their work, Team W and Team X created strains of influenza that were more pathogenic than their original influenza stocks. Such research can be useful for understanding evolutionary pathways of viruses, which in turn can inform surveillance, testing and therapeutic development, but it also creates higher risks. If the new strains were to infect laboratory staff, that could pose a risk not only to an individual's health but also to broader public health because

it could seed an outbreak. The same information that could help to inform public health surveillance could also be misused by nefarious actors hoping to create more dangerous pathogens themselves.

Team W, which is based in Country A, decided to seek a collaboration with Team X, which is based in Country B and has limited regulation on DURC. If the in vivo research was deliberately done in Country B to avoid the stricter regulations of Country A, this would be considered as unethical research, a practice also referred to as ethics dumping (12).

Priority actions, tools and mechanisms highlighted by Scenario 7, for selected stakeholders to consider (other actions, tools and mechanisms, and stakeholders may also arise)

International organizations

- » Create international guidelines for responsible life sciences research. An international minimum standard for oversight of life sciences research would ensure that the research of Team W and Team X had some biosafety and biosecurity guidelines applicable to the work in each country. Adopting an international minimum standard could also help countries to streamline the development of their own, more comprehensive governance mechanisms with other countries, to create a simpler regulatory environment for scientists and their institutions.

Institutions and PIs

- » Create training modules required for all team members. All team members should receive thorough training on how to assess the risks of the work, appropriately implement mitigation measures, and safely and securely conduct the work.
- » Ensure all team members working on the project have training in biosafety and biosecurity, regardless of the individual's home institution.

Governments of Country A and Country B

- » Have guidance for safe and secure life sciences research, especially research with potentially high-consequence pathogens (based on an international minimum standard for oversight of life sciences research). Guidelines for such research, including the dual-use guidelines of Country A, should be regularly reviewed for gaps in oversight, and revised as needed. Once it becomes apparent that potentially high-consequence work is being exported to another country, governments should work together to address any gaps in oversight.

Institutions of Team W and Team X and biosafety officers

- » Ensure the work conducted by their researchers is in accordance with all international, national and local regulations.
- » Help the teams conduct risk assessments and implement mitigation measures. The institutions should also be aware of the collaboration. The institution of Team W should make sure that their collaboration and export of samples to Team X is not prohibited by laws in Country A or Country B.

Team W and Team X members

- » Conduct the research with the novel influenza pathogen. They are responsible for understanding the risks associated with the work and the biosafety and biosecurity protocols in place to mitigate the risks. They are also responsible for conducting the research ethically and legally.

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Annex 2. Case studies for responsible life sciences research on high-consequence pathogens²⁷

²⁷ This annex provides three case studies that draw directly on the case studies developed in the report titled Biosecurity and Health Security Protection (BSP) Case Studies WHO Framework for Responsible Life Science Research (unpublished).

Case study 1

Chemical synthesis of poliovirus cDNA

In 2001, a researcher in the USA announced that his laboratory had synthetically created a full-length poliovirus complementary DNA (cDNA) construct without the use of living cells, template DNA or template RNA. Results of this work were published in the journal *Science* in 2002 (1), marking the first publication for chemically synthesizing a virus de novo. At that time, the work was flagged within the virology and biosecurity communities as potentially problematic, and it sparked a debate about whether the work should be conducted and, if so, how it should be published, if at all.

The lead researcher for this work was originally trained as an organic chemist before venturing into virology. In 1991, his laboratory published the empirical chemical formula of poliovirus in an article (2) that argued that viruses were non-living entities – specifically, that they were chemicals that had a life cycle – a view he maintains today (3). To complete this work in 1991, the laboratory synthetically created the poliovirus using template RNA from an already existing poliovirus but without the use of living cells. To support the argument that viruses were chemicals rather than living entities, the laboratory wanted to demonstrate that a functional virus could be synthesized without the use of living cells or template genetic material.

The sequences of many viruses, including the poliovirus, are publicly available online. To complete the de novo chemical synthesis, researchers used the publicly available sequence to create their synthetic virus. The laboratory segmented the poliovirus sequence into fragments with an average length of 69 nucleotides. These sequence fragments were then ordered from a commercial company that creates synthetic genes for customers based on supplied sequences. The company then shipped the synthesized fragments, called oligonucleotides, to the laboratory. Once the laboratory had the oligonucleotides, the fragments were combined and sequenced. The laboratory found they had successfully created a full-length cDNA for poliovirus.

To test whether the cDNA strand they had synthesized could create functioning virus proteins, the team transcribed the cDNA into RNA and then incubated the transcribed RNA with cytoplasmic extracts from an uninfected human cell line. The incubation mixtures were then applied to human cells to determine whether the transcribed and translated RNA produced infectious virus particles. The incubation mixtures were able to infect the human cell line, confirming that the synthesized cDNA could create infectious poliovirus in cell culture. To confirm that the synthesized cDNA could create poliovirus that was pathogenic in animals, the laboratory injected the incubation mixture into transgenic mice to assess whether the synthetically derived viruses displayed altered pathogenicity to wildtype virus. The team found similar pathology between the chemically derived virus and the wildtype virus, although the chemically derived virus required higher doses to cause death compared with the wildtype viruses.

In 2002, several publications commented on this experiment. Some people in the security community and publics criticized the publication of the work as giving bioterrorists the tools they need to create a bioweapon (4, 5, 6); for example, enabling someone with malicious intent to synthetically create smallpox or Ebola viruses. The lead researcher said that his work highlighted the risks of having virus sequences publicly available, because anyone could make any virus from published data; he also said that his work was not contributing additional risk because others had previously published the fact that this was theoretically possible (7, 5). There was disagreement over the amount of risk the publication actually posed; poliovirus would be relatively easy to synthetically create without templates or human cell lines owing to its relatively small, unsegmented genome. Viruses with larger, more complex genomes would be much harder to synthesize using the approach published. There was also concern (5) among viral geneticists that the publication and its surrounding controversy could cause the US government to implement new restrictions on research, especially considering the anthrax attacks that occurred a year earlier in 2001.

In addition to questions about whether this work should have been completed and published, there was also concern (8) that the publication included no discussion of the ethics or risks associated with the work. The lead researcher for this experiment later published a manuscript (9) discussing the controversy surrounding his work, in which he explained that his team originally included a discussion of ethics and security risks, but the editors at *Science* demanded those sections be removed. *Science* defended publishing the manuscript because it had been through the usual peer-review process at the time. There was also no external ethics review before the experiments started (4). The funder of the work was the US Department of Defense, via

the Defense Advanced Research Projects Agency (DARPA) (10). The lead researcher later reported that no one approached him or his team about the 1991 paper that described synthesized poliovirus using cell-free extract. He also said that Science did not raise any security concerns over the 2002 publication (10).

Since this 2002 publication, synthetic biology technology has rapidly advanced. There are more people than ever working in synthetic biology, there has been an explosion in the number of DNA synthesis companies from which oligonucleotides can be ordered, and many more viruses have been synthetically generated or modified. However, there have also been several changes in how such research is governed by several stakeholders. In 2003, several editors from life science journals released a statement discussing biosecurity and how their journals would start reviewing manuscripts for biosecurity risks (11). In the USA, the PATRIOT Act made it a criminal offence to knowingly possess a biological agent in a quantity that could not reasonably be for peaceful purposes. A 2004 report (12), commonly known as the “Fink report” – published by the US National Research Council’s Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology – recommended that the US Department of Health and Human Services create a new review system for seven categories of experiments regarding microbial species, in addition to the recombinant DNA reviews conducted by the US National Institutes of Health (NIH) (implemented in 1976) (13) before experiments begin. The 2004 report also recommended that the Department of Health and Human Services create a National Science Advisory Board for Biodefense, which would review proposals or manuscripts, serve as a resource to the US government concerning biosecurity risks and periodically review governance measures related to biosecurity.

Since 2002, the editors of many major high-impact scientific journals have instituted new mechanisms to review submitted manuscripts for security risks and to consider what ethical or contextual information should be included in publications for responsible reporting of the work. The US Department of Health and Human Services also created the National Science Advisory Board for Biosecurity (NSABB), which subsequently created several documents regarding governance and oversight of dual-use life sciences research (14). Policies such as the 2012 *US Government policy for oversight of life sciences dual use research of concern* (15), the 2014 *US Government policy for institutional oversight of life sciences dual use research of concern* (16) and the 2017 *Recommended policy guidance for departmental development of review mechanisms for potential pandemic pathogen care and oversight (P3CO)* (17) have been adopted to reduce biosecurity risks associated with research with certain pathogens.

Limitations and gaps in governance of research such as that conducted in the 2002 paper continue in the USA. Although the NSABB has previously been active in reviewing and advising on biosecurity considerations, the board has not met since January 2020, and before that meeting it last met in 2017. The 2012 DURC (15) and 2017 P3CO (17) policies do not cover all research of potential concern, including the work done in the 2002 paper, because poliovirus is not on either policy's list of agents. Not all journals have the expertise in-house to conduct thorough reviews for potential biosecurity risks. Both within the USA and internationally, the debate on how to best address governance of life sciences research continues.

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Case study 2

Spanish influenza reconstruction

In 2005, a group of scientists from the US Centers for Disease Control and Prevention (CDC), the Mount Sinai School of Medicine, the Armed Forces Institute of Pathology and the US Department of Agriculture (USDA) worked together to generate a reconstruction of the 1918 pandemic influenza virus (1). The reconstruction study was published in the journal *Science* in October 2005 (1). Coding sequences published in prior literature were used to rebuild each gene of the 1918 pandemic influenza virus, and the virus was reconstructed from those genes using a reverse genetics system, followed by an infectious virus being generated in cell culture (1-8).

Once the 1918 pandemic influenza virus had been reconstructed, the scientists tested it for infectivity, pathogenicity and viral growth. Infectivity of the virus was examined in mammalian cells in both the presence and absence of trypsin (1). Growing the virus in the presence and absence of trypsin is important because the capacity of an influenza virus to replicate in vitro without trypsin to cleave the haemagglutinin (HA) molecule is commonly believed to be a determinant of pathogenicity in mammals (9, 10). The study determined that the 1918 pandemic influenza neuraminidase (NA) protein was responsible for cleavage of the HA protein in the absence of trypsin, but the mechanism for this action was not similar to previously studied influenza viruses (1).

Pathogenicity was examined through infection of mice with the reconstructed 1918 pandemic influenza virus (1). The intranasal infection resulted in high viral titres in the lungs, high lethality and rapid weight loss (1). The animal study was able to determine that the virus did not spread to the brain, heart, liver or spleen and that the development of severe lesions in the lungs was caused by a mechanism related to the 1918 pandemic influenza HA gene (1).

The growth of the virus was examined through the infection of a polarized human lung epithelial cell line (1). Titres of the 1918 pandemic influenza virus were primarily found on the apical side of the cell, and they were significantly higher than any of the control viruses tested (1). The results of this experiment were twofold; they showed that the HA and polymerase genes were responsible

for optimal virus replication in lung epithelial cells and they confirmed that high viral titres are present in the lungs during infection (1).

The work performed in the 1918 Spanish influenza reconstruction study was quickly scrutinized by other scientists and publics, but researchers preemptively provided a list of justifications for what could be seen as a risk-intensive project. The primary justification provided by the authors included the beliefs that a future influenza pandemic is likely, that better understanding of the 1918 pandemic influenza virus could aid our understanding of potential novel influenza viruses, and that the research could identify targets for therapeutic development (1, 11). The justification that a future influenza pandemic is possible is supported by an Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services report claiming that future pandemics are likely to emerge more often and spread quickly because of factors such as the disruption of ecosystems and the proximity of humans to wildlife (12). Despite increases in influenza surveillance, the emergence of an entirely new strain of influenza with pandemic potential is still possible (13).

The second justification from the authors was that a better understanding of the 1918 pandemic influenza virus could aid our understanding of potential novel influenza viruses that may emerge in the future (1). One of the key findings from the 1918 Spanish influenza reconstruction study was that the NA protein was responsible for the cleavage of the HA protein through a mechanism that had not been identified previously (1). The discovery of a novel mechanism had the potential to open a new avenue of research, which could put the field a step ahead of a novel influenza virus that uses the same HA cleavage mechanism. The final justification was that the research could identify new targets for therapeutic development (1). The study identified that the HA and polymerase genes were important virulence factors, and subsequent research has focused on the development of polymerase inhibitors (1, 14, 15). Viral polymerase inhibitors could be a crucial therapeutic, should a 1918 influenza or novel influenza A pandemic occur in the future (15).

Critics of the 1918 Spanish influenza reconstruction study expressed concerns that the published article could serve as a blueprint for malicious actors to construct a bioterrorism agent owing to the detailed methodology and the public availability of the viral genome (16). Additional criticisms claimed that the benefits of reconstructing a virus with such a deadly history are not well defined and that there are plenty of other influenza viruses that could be studied for the purposes of pandemic preparedness (16). The NSABB reviewed the article and unanimously voted to endorse publication (17). However, the board stated that the decision was made to encourage further research in

the field of influenza pandemic preparedness and that the risk of misuse was outweighed by the potential benefits to scientific understanding (17, 18). The criticism that the benefits of reconstructing the 1918 Spanish influenza virus were not well defined are partially addressed by the improvements in influenza pandemic preparedness that resulted from the discovery of novel mechanisms, virulence factors and drug targets, although the threshold for what level of benefit outweighs the risk will change between stakeholders (1, 14, 15). The criticism that there are other influenza viruses that could be examined to achieve the same goals sought by this study was also partially addressed by the discovery of a new mechanism for NA cleavage of HA, which was only possible using the full-length 1918 reconstruction, because this mechanism had not been observed in any other influenza viruses (1, 19). However, it is possible that this mechanism could have been discovered in a different influenza virus if the proper screening had been performed.

Support and funding for the 1918 Spanish influenza reconstruction process were provided by the USDA, NIH, Armed Forces Institute of Pathology and CDC (14). The reconstruction of the virus was performed at CDC facilities (14). The CDC required that the project be approved by an institutional biosafety committee and an animal care and use committee before work was allowed to commence (14, 20). The committees sought to mitigate risk by ensuring that all work with any virus containing one or more genetic elements from the 1918 Spanish influenza virus be performed in a Biosafety Level 3 laboratory with enhancements (BSL3-E) (14, 20, 21). The viruses were handled in a manner consistent with recommendations from the US Federal Select Agent Program, even though the 1918 Spanish influenza virus was not registered as a select agent when the research occurred (14, 22). Only one scientist was allowed to access the laboratory during the reconstruction process, and that scientist was taking a daily prophylactic antiviral agent to mitigate infection risk. No other influenza viruses could simultaneously be handled in the same laboratory as the 1918 Spanish influenza virus, to prevent cross-contamination, and the scientist worked with the understanding that he would be placed in quarantine if he became infected with the virus (20).

The journal *Science* consulted with external experts who had experience in the field, and asked the authors to discuss their results with federal officials before the publication was released (23). The debate around whether the results should have been published ranged from concern over the publications being used as a blueprint for bioterrorism to declarations that scientific journals had the right to publish whatever content they wished under the protection of the first amendment (16, 23).

Current government policies that may govern the types of research performed in the 1918 Spanish influenza reconstruction and characterization project include the *US Government policy for oversight of life sciences dual use research of concern* (24), the *US Government policy for institutional oversight of life sciences dual use research of concern* (25), the *Recommended policy guidance for departmental development of review mechanisms for potential pandemic pathogen care and oversight (P3CO)* (26), and the *Select agent and toxins regulations* (21). The US DURC policies establish a review mechanism for certain research at federally funded institutions with certain pathogens that could potentially be misused by malicious actors. The DURC policies address research that generates or reconstitutes an eradicated or extinct agent or toxin listed in the policies (24). The *Recommended policy guidance for departmental development of review mechanisms for potential pandemic pathogen care and oversight (P3CO)* requires federal agency review and oversight of federally funded research that is anticipated to create, transfer or use enhanced pathogens with pandemic potential (26). The reconstructed 1918 Spanish influenza virus was added to the *Select agent and toxin regulations* list after the research was published (21). As a result, all research involving the virus must meet the standards of the Federal Select Agent Program (21).

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Case study 3

Environmental surveillance for Nipah virus

Environmental surveillance of infectious diseases is a process that can involve collecting biological samples from humans or local animal populations, or directly from surfaces. Environmental surveillance of infectious diseases is often used (1) to monitor risk areas for disease and identify risk factors for pathogens spilling over into a human population. The goal of collecting environmental surveillance data typically involves preventing future outbreaks caused by a spillover event. The transmission of an infectious disease from an animal population into a human population is commonly known as a zoonosis (2). The rate at which new diseases emerge has increased because of factors such as global climate change and human encroachment into previously unsettled territories (3). About 60% of all novel emerging infectious diseases are the result of zoonoses (4).

Nipah virus is the infectious agent behind a zoonotic disease characterized by cough, fever, headache and vomiting, with coma, confusion, encephalitis and even death occurring in more severe cases (5). Outbreaks of the disease are believed to originate with transmission of Nipah virus from *Pteropus* bat species to humans through the consumption of bat secretions in fresh date palm sap (6). As a result, numerous efforts have been made to perform environmental surveillance of Nipah virus in *Pteropus* bat species in Bangladesh (7, 8). The goals of these previous studies were to characterize the dynamics of Nipah virus in its natural reservoir over space (7) and time, and to characterize the nucleocapsid protein evolution over time (8).

Environmental surveillance of Nipah virus has been performed through two primary methods in recent years. The first method involved placing tarpaulins below the roosts of *Pteropus medius* bats to collect urine (8). Urine samples were pooled in the tarpaulins and collected in 50 mL Falcon tubes. Limitations of the first method include the inability to guarantee that all samples are from *P. medius* bats and the dilution of Nipah virus positive samples with negative ones. The second method involved capturing individual bats in custom-made nets attached to treetops near *P. medius* roosts (7). The bats were removed

(by people wearing adequate PPE), then anaesthetized and taken to a field laboratory for sampling. Weight, age and sex were recorded for each captured bat, then blood samples, throat swabs, wing biopsies and urine samples were collected. Potential limitations of the second method include a greater risk of infection for the field researcher owing to the handling of a live wild animal.

Justifications for performing the environmental surveillance research included determining the risk of viral spillover into human populations, better understanding of the determinants of viral transmissibility, providing molecular targets to better gauge the pandemic potential of Nipah virus in environmental samples, and targeting interventions to prevent a spillover event from turning into a global pandemic. The studies were able to partially support their justifications (7) by determining that Nipah virus transmission is not exclusively confined to a region previously known as the “Nipah Belt” (9) between November and April. This information highlights that public health officials may need to look at herd immunity levels in *P. medius* populations around Bangladesh (rather than certain calendar dates in a specific region) when implementing spillover prevention interventions. The studies were also able to partially support their justifications (8) by characterizing the evolutionary rate of the Nipah virus nucleocapsid gene. In the 2021 publication, the authors claimed that this information will help to determine whether an environmental sample of Nipah virus has pandemic potential, but the article calls for future studies to better understand outbreak risks (8).

Criticism of environmental surveillance research tends to focus on the risk posed to society if a field researcher is infected with a pathogen with pandemic potential. The risk of viral exposure is most prevalent when collecting samples directly from living wild animals. These risks can include needle sticks while taking blood samples, exposure of animal excreta to open wounds, and bites or scratches from improperly anaesthetized animals. The first environmental surveillance collection method (8) limits the risks posed by needle sticks and bites or scratches, but the data quality is sacrificed as a result. Lower data quality may reduce the impact the study results can have on preventing or mitigating Nipah virus spillover events. The second environmental surveillance collection method (7) produces high-quality and specific data, but the risk to field researchers is considerably increased. The unintentional infection of a researcher with Nipah virus has the potential to result in a global pandemic if proper precautions are not followed. The study that used the second environmental surveillance collection method did follow proper precautions – all researchers were equipped with nitrile gloves, P100 respirators, safety glasses, Tyvek suits and welding gloves while handling the bats. The use of this PPE can greatly reduce the risk of infection, but it does not completely eliminate the potential threat to the researcher or society at large.

International guidance on how to perform environmental surveillance research in a safe and efficacious manner is limited. The 4th edition of the WHO *Laboratory biosafety manual (10)* contains a section that advises researchers to treat all collected materials as potentially infectious when performing environmental surveillance in a disease outbreak situation. This advice was followed by the researchers performing the second environmental surveillance collection method (7) since they wore adequate PPE while handling all bats; however, more specific international guidance related to environmental surveillance research in non-outbreak scenarios is needed. Continual medical surveillance of all researchers during and after sample collection events, the use of adequate PPE to avoid exposure to potentially infectious animals or biological materials, and making an effort to minimize sample collection events without sacrificing data quality should be considered the minimal standards for safe environmental surveillance research. Where possible, pre-exposure preventive treatments should be used during environmental surveillance.

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Annex 3. Illustrative examples of awareness raising, education, training and capacity-building in the life sciences and related fields²⁸

²⁸ This annex provides examples from various countries and is based on the WHO publication *Towards a global guidance framework for the responsible use of life sciences: summary report of consultations on the principles, gaps and challenges of biorisk management (1)*.

Argentina

The Argentine National Authority for the Chemical Weapons Convention developed a national project on education and outreach to improve the level of knowledge about the role of the treaty and the national legislation that implements it; raise awareness about the dual-use nature of knowledge in the chemical sciences and the risks that it implies; and promote a culture of responsible use of technical and scientific knowledge (2). These efforts were taken up by, for example, the chemistry department at the University of Rosario, where chemical safety, security and responsible conduct of science are part of the chemical curricula, with various curricular activities, elective subjects (e.g. bioethics, green chemistry and educating for a sustainable future) and complementary activities (e.g. workshops and seminars). New activities are being designed to improve discussion of these topics in the curriculum, with evaluation of their impact in a research project financed by the university.

Australia

The Biosecurity Emergency Response Training Australia (BERTA) was established through a collaboration between several Australian state and territory governments, the Commonwealth, Animal Health Australia and Plant Health Australia (3). To maintain consistency in biosecurity training, the National Biosecurity Committee funded Tocal College to develop the BERTA training and assessment materials.

Canada

Several governmental agencies – for example, the Centre for Biosecurity of the Public Health Agency of Canada and the Office of Biohazard Containment and Safety of the Canadian Food Inspection Agency – have developed biosafety and biosecurity training materials, as well as an online training portal.

Tri-agency framework: Responsible conduct of research is a key reference document for the three major Canadian funding agencies (4). It guides all funded research as well as research institutions eligible for funding. The framework sets out the responsibilities and corresponding policies for researchers, institutions and the agencies, to support and promote a positive research environment.

China

The *Tianjin Biosecurity Guidelines for Codes of Conduct for Scientists* (5) are high-level principles that serve as a reference for a broad range of stakeholders to develop or amend national-level or institutional-level codes of conduct, practices, protocols or regulations. Inspired by the Hague Ethical Guidelines, which were developed by the Organisation for the Prohibition of Chemical Weapons, the Tianjin Biosecurity Guidelines emerged from work by China and Pakistan, and were developed collaboratively by InterAcademy Partnership leaders, Tianjin University's Centre for Biosafety Research and Strategy and Johns Hopkins University's Center for Health Security, with input from scientists from 20 different countries.

France

Established in 2011, the Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) [National Agency for the Safety of Drugs and Health Products] aims to ensure the safety of medicines and health products and to support health policy decision-making for the safe use of drugs and biological products. It is responsible for the inspection of manufacturing sites of medical and health products; it also regulates and inspects work with microorganisms and toxins. The National Consultative Council for Biosecurity (CNCB) was created in 2015 (6) to develop guidance to mitigate misuse of dual-use research in the life sciences.

Germany

The German Research Foundation (DFG) and the Leopoldina (German Academy of Sciences) established the Joint Committee on the Handling of Security-Relevant Research to raise awareness among researchers of dual-use issues in security-relevant research, and to further develop and foster a responsible approach to security-relevant research and self-governance within the research community (7). DFG and Leopoldina also issued a code of conduct on “Scientific Freedom and Scientific Responsibility”; scientists applying for funds must commit themselves to that code. The Joint Committee is promoting the establishment of committees for ethics in security-relevant research (KEFs) at individual German research institutions for guiding their work. The Joint Committee provides assistance in dealing with questions on related issues and serves as a platform for sharing experiences, by organizing workshops, and awareness-raising and horizon-scanning activities.

The Federal Foreign Office established the German Biosecurity Programme in 2013 (8). Its aims include preventing the misuse of pathogens and toxins, limiting the availability and dissemination of dangerous pathogens, and strengthening the national health capacities of partner countries. The programme comprises several individual projects that are implemented in cooperation with German institutions, including the Robert Koch Institute. The programme emphasizes activities in Africa and Central Asia, including training programmes such as the Global Partnership Initiated Biosecurity Academia for Controlling Health Threats (GIBACHT) (9) and the development of surveillance and diagnostic systems in partner countries. Also, member organizations raise awareness in the scientific community by devoting sessions of their scientific conferences to the topics biosecurity and dual-use research (e.g. (10)).

All research activities on genetic modification with high-consequence pathogens (Biosafety Levels 3 and 4) need to be reviewed by a national honorary expert panel, the Central Committee on Biological Safety (ZKBS) (11). The ZKBS advises on safety and containment measures to be taken during genetic engineering operations. For lower risk activities, a ZKBS opinion is mandatory if risk assessment is uncertain. Also, the ZKBS was mandated by the Federal Ministry of Food and Agriculture to perform a horizon scan on developments in synthetic biology, to identify potential biosafety threats and gaps in legislation.

Scientific societies such as the German Society for Virology (GfV) are also guiding activities for awareness raising. The GfV Commission “Virological Research with Dual-Use Potential” informs the virological scientific community about new developments and regulations. It also aims to raise awareness among young scientists in the field of virology about freedoms and responsibilities in science.

India	In 2017, the Indian Council of Medical Research issued the revision of its <i>National ethical guidelines for biomedical and health research involving human participants</i> (12). The guidelines have a section on responsible conduct of research. It had also made guidelines for conduct of scientists experimenting on biorisk materials.
Japan	The Science Council of Japan revised its code of conduct for scientists in 2013 and included a clause on DURC. In response, the following year, the Subcommittee on Pathogens Research made recommendations on dual-use issues related to infectious disease research, noting the importance of awareness-raising and educational activities in academia. In 2015, with the support of a grant-in-aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology, the Biosecurity Study Group was established to conduct research, education and awareness-raising activities related to biosecurity. The Association for the Promotion of Research Integrity, founded in 2016, has been providing online educational modules in both Japanese and English, part of which includes education on biosecurity.
Kenya	In addition to training in safety, over the past 5 years, the Kenya Chemical Society has conducted chemical security training and outreach campaigns in academia and industry. These have revealed insufficient basic knowledge among chemical practitioners about chemical security to prevent misuse, theft and diversion of hazardous and dual-use chemicals (13).
Lebanon	Several biosafety and security-related initiatives have been undertaken in Lebanon, including the establishment of a biosafety and biosecurity association (14), and outreach to perpetuate responsible science concepts. The outreach initiatives have primarily targeted faculty and students and trainees at universities and hospitals; they have provided education on basic biosafety principles and biosecurity measures through seminars, symposia, poster sessions, workshops, online courses and forums, as well as train-the-trainer events.
Malaysia	The responsible conduct of research (RCR) education agenda in Malaysia was initiated by the Educational Institute on Responsible Science in Kuala Lumpur. In collaboration with the US National Academies of Sciences, Engineering and Medicine, and with support from the Malay Ministry of Education, the Young Scientists Network of the Academy of Sciences Malaysia produced the first Malaysian educational module on RCR, including a chapter on the culture of safety and dual-use research, in 2018 (15). In 2019, sponsored by the International Science Council, the 2-year Association of Southeast Asian Nations (ASEAN) RCR programme was initiated to train the first cohort of ASEAN RCR instructors (16).
Mexico	The Mexican Biosafety Association (17) was established in 2009 as a member of the International Federation of Biosafety Associations. Its aim is to provide information on biosafety and biosecurity and to promote training in these fields.

Morocco	The Moroccan Biosafety Association (18), in partnership with the US Biosecurity Engagement Program, the Task Force for Global Health and Gryphon Scientific, organizes biosafety and biosecurity training workshops, meetings and train-the-trainer events.
The Netherlands	<p>The Dutch government established a biosecurity office in 2013 as an information centre for biosecurity (19). The office collaborates with many international organizations, and an internal working group provides lectures, webinars and workshops, as well as tools and web applications that provide biosecurity education and help to identify potential biorisks. The office also organizes an annual biosecurity knowledge day.</p> <p>At the request of the Dutch Ministry of Education, Culture and Science, the Royal Netherlands Academy of Arts and Science (KNAW) developed a Code of Conduct for Biosecurity (20). The code aims to prevent direct or indirect contribution of the life sciences or their application to the development, production or stockpiling of biological weapons (as described in the Biological and Toxin Weapons Convention), or to any other misuse of biological agents and biological material.</p>
Pakistan	In collaboration with other countries, Pakistan has been carrying out awareness-raising activities and producing educational materials on bioethics, biosafety, biosecurity and dual-use research since 2010 (21). These activities are aimed at strategizing and promoting awareness of biorisk management in Pakistan, and they emphasize a “holistic biosecurity” approach that is not limited to laboratories.
Ukraine	In 2018, the Organization for Security and Co-operation in Europe conducted a thorough review of biological safety and security in Ukraine and identified major gaps, one of which was appropriate training in biosafety and biosecurity. Several projects were launched to address these gaps, including training and raising awareness for life scientists. In 2019, the Council of the European Union issued a decision to support strengthening of biological safety and security in Ukraine, including awareness raising, education and training (22).
United Nations Interregional Crime and Justice Research Institute	The United Nations Interregional Crime and Justice Research Institute (UNICRI), in collaboration with the US Federal Bureau of Investigation (FBI), administers the International Network on Biotechnology (INB). The INB is a global network of academic and research institutions that is committed to advancing education and raising awareness about responsible and secure conduct in basic and applied life sciences (23). The INB also supports the development and sharing (via an online portal accessible to network partners) of modular educational resources (e.g. awareness-raising videos, scenarios and active learning exercises) covering the themes of biosafety, biosecurity and bioethics.

United Kingdom of Great Britain and Northern Ireland

In the United Kingdom of Great Britain and Northern Ireland (United Kingdom), the International Biological Security Programme (IBSP) aims to prevent the acquisition and hostile use of human, animal and plant pathogens and associated technologies, and to reduce risks to the United Kingdom and its international partners through scientific cooperation. The IBSP will also continue to implement international security elements of the United Kingdom's National Biosecurity Strategy.

The IBSP supports cooperative international biological security activities that reduce the threat of deliberately caused disease events, and the risks and impacts of naturally occurring or accidental disease outbreaks. The programme aims to provide assistance with the development of effective pathogen security, biosafety, diagnostics and disease surveillance capabilities in partner countries. This includes addressing international concerns related to dual-use science and potential misuse, strengthening nonproliferation awareness, and improving opportunities for technical collaboration, assistance and capacity-building through cooperative activities. The IBSP focuses on sustainability and the development locally of appropriate capacities, including through innovation and applied research projects.

The University of Bath and the company Biosecure developed an online training course "Next generation biosecurity: responding to 21st century biorisks", which has been available worldwide since 2018 on the platform FutureLearn. Over several weeks the course explores biosecurity and how to respond to biological threats, covering biosecurity, biosafety and bioethics.

The University of Bradford has produced an education module resource, *Preventing biological threats: what you can do* (24) and *Biological security education handbook: the power of team-based learning* (25). London Metropolitan University has produced an innovative set of biological security education cartoons (26). These products are available in several languages.

United States of America

The US Department of State Bureau of International Security and Nonproliferation Office of Cooperative Threat Reduction initiated the Biosecurity Engagement Program (BEP) in 2006. This programme has supported training activities and other capacity-building efforts to promote biosafety and biosecurity best practices, prevent misuse in the life sciences, and prepare partners to detect and respond to high-consequence pathogen disease outbreaks. Since 2010, BEP has supported several institutions committed to advancing awareness raising and education about responsible and secure conduct in the life sciences. For instance, BEP supported three international meetings on conducting responsible science in the Middle East and North Africa (MENA) region, and workshop training on responsible conduct of science and bioethics for stakeholders working in the life sciences. BEP also supported several workshops on biosafety and biosecurity in the MENA region. The outcomes included the development of modular educational resources including biorisk assessment videos and scenarios, and a mock research review exercise focused on identification and analysis of risks and benefits of research activities. This programme also supported an online course on biorisk management accredited by the International Association for Continuing Education and Training across MENA countries.

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