STANDARDS FOR FUNDERS AND GRANTEES TO IDENTIFY AND MITIGATE BIOLOGICAL RISKS

Wellcome Trust and NTI | bio co-authored this paper informed by discussions held under Chatham House Rule at a meeting organized by NTI | bio, Wellcome Trust, and the World Economic Forum. It contains ideas discussed during that meeting regarding policies for engaging funders and building risk evaluation into research and development (R&D) grant proposals.

Urgency: During a June 2018 meeting hosted by the Wellcome Trust and co-sponsored by NTI and the World Economic Forum in London, experts raised concerns about the lack of requirements for grantees to recognize and consider minimum biosecurity standards and evaluate potential risks associated with research and new technology developments in synthetic biology, genomics, virology, and related fields. The assembled group proposed the development of a new, globally-adopted standard process to enable grantees to assess risk and propose mitigation strategies within submitted proposals and through the duration of the research.

Concept: There is no doubt that advances in genomics, synthetic biology, and virology will prove essential to achieving a safer and more secure society. However, as recent discussions[1] around the *de novo* synthesis of an extinct horsepox virus[2] demonstrate, emerging biotechnologies also have the potential to enable research that could benefit a nefarious actor or lead to an accidental release of a harmful biological agent. Existing national guidelines to oversee research that creates and modifies pathogens are fragmented and do not adequately consider the global and changing nature of life science research collaborations. Many countries place safety and security controls on dangerous infectious agents but do not provide guidelines for assessing the aims, outcomes, or risks of research experiments to make, modify, or enhance transmissibility or virulence of them. Others recommend self-governance or provide guidance, but do not have laws or regulations in place[3]. And others, such as the United States, use the Fink Report's[4] seven specific classes of experiments as a guide and then apply oversight requirements when those experiments are conducted with specific agents. Such mechanisms do not provide a comprehensive, future-proof approach that encourages a sufficiently robust biosecurity risk evaluation for considering consequences to third party nonparticipants born out of high-risk biological research[5].

Just as biosafety levels are now an internationally accepted norm, so too should biosecurity risks be identified with multiple gradations and mitigated through established best practices as researchers design experiments and submit funding proposals. We

[1] Koblentz GD (2017). The *de novo* synthesis of horsepox virus: implications for biosecurity and recommendations for preventing the reemergence of smallpox. Health Security (15)5, 620-628. http://doi.org/10.1089/hs.2017.0061.
[2] Noyce RS, Lederman S, Evans DH (2018). Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments. PLoS ONE 13(1): e0188453. https://doi.org/10.1371/journal.pone.0188453.
[3] Millet PD (2017). Gaps in the International Governance of Dual-Use Research of Concern. *National Academies*. January
[4] U.S. National Academies National Research Council (2004). *Biotechnology Research in the Age of Terrorism*.
[5] Eyal N, Lipsitch M, Bärnighausen T, Wikler D (2018). Risk to study nonparticipants: A procedural approach. PNAS 115(32) 8051-8053. https://doi.org/10.1073/pnas.1810920115

propose to explore the development of a new mechanism for researchers and funders to mitigate biosecurity risks, which would include a process for: (1) identifying and assessing potential biosecurity risks during the design of experiments; (2) Transparently sharing the strategies identified within funding proposals for mitigating those risks; and (3) developing explicit procedures to consider whether the risks remaining after mitigation are justified by the potential benefits of the work. This approach builds on other mechanisms that seek to standardize considerations for biotechnologies with the potential for misuse such as the safety form for the Internationally Genetically Engineered Machine (iGEM) competition[6], the Wellcome Trust's Dual-Use Statement[7], and the principles for sponsors and supporters of gene-drive research[8]. These are briefly outlined below and could be the starting place for the creation of a new common mechanism for funders and grantees to identify and mitigate biological risks. Such a mechanism should explicitly address:

- the responsibility of each researcher to evaluate the potential for accidental and intentional misuse of biotechnology in their work;
- the need for a funder-driven approach to guide the grant process and foster risk evaluation; and
- the requirement for a dynamic repository of best practices for risk mitigation to aid in a comprehensive risk-benefit analysis.

Principles for gene drive research (2017)

Drafted in response to a 2017 report that provided recommendations for responsible research on gene drive technologies by U.S. National Academies of Science, Engineering, and Medicine (NASEM)[9], the principles for gene drive research acknowledge the role of researchers and sponsors as stewards of science and the public trust in the technology. Accordingly, the principles support risk assessment and management in all phases of research, as well as supporting opportunities to partner, educate, and train both researchers and the public alike. The nature of gene drives focuses the principles on the ecological risks that come with the release of this technology, which is essential when evaluating the research on any biotechnology to be used at the population scale or that might proliferate in an undesirable way.

BBSRC[10], MRC[11], and Wellcome Trust position statement on dual use research of concern and research misuse (2015)

This statement outlines a mechanism for oversight of a specific avenue of biological research that can be misused to cause harm. While some countries have already

[6] 2018 iGEM Safety Form, retrieved 10 October 2018 from http://2018.igem.org/Safety/Final_Safety_Form.
[7] BBSRC, MRC and Wellcome Trust position statement on dual use research of concern and research misuse, retrieved 10 October 2018 from https://wellcome.ac.uk/sites/default/files/wtp059491.pdf.
[8] Emerson C, James S, Littler K, Randazzo F (2017) Principles for gene drive research. Science 358(6367), 1135-1136. https://doi.org/10.1126/science.aap9026.
[9] National Academies of Sciences, Engineering, and Medicine (2016). Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. Washington, DC: The National Academies Press. https://doi.org/10.17226/23405.
[10] Biotechnology and Biological Sciences Research Council
[11] Medical Research Council

adopted governmental policies addressing dual-use research of concern, this funder-driven statement highlights the need for a more consistent global approach to evaluating research risks[12]. The statement acknowledges the difficulty in identifying projects with the potential for misuse, however it includes the expectation that researchers will update funders as they make changes to the experimental protocol and encourages funders to be the proactive leaders of global dual-use risk evaluation. Furthermore, it identifies the key elements needed for effective self-governance: funders, individual researchers, and research communities working together to identify, prepare for, and respond to dual-use biosecurity risks.

iGEM Safety Form

Participants in the iGEM competition use a standard kit of interchangeable parts to build novel biological systems. Each team that enters the competition is required to complete a thorough safety form that guides them through the process of both identifying and mitigating risk. iGEM analyzes the risks and benefits of each project and determines whether it will allow the team to participate in the competition. This standardized mechanism for risk evaluation allows iGEM to monitor participants before and throughout their projects to ensure they are considering and mitigating risk. To better utilize this information, one could create a dynamic repository of safety considerations to be used to continuously update the safety form based on advances in technology. Such a repository should be informed by researchers and maintained by a consortium of funders dedicated to the sponsorship of safe biological research. This could create a web of researchers, funders, and experimental protocols to standardize risk-benefit analyses.

Example Approach to Minimize Emerging Technology Risks from another Field: The Institute of Electrical and Electronics Engineers (IEEE) recognized the public risk associated with the increasing influence of artificial intelligence systems without deliberate efforts to ensure the technologies serve humanity's values and principles. To address this, the IEEE Global Initiative on Ethics of Autonomous and Intelligent Systems[13] published a document, *Ethically Aligned Design,* that identified pertinent issues and with the goal of fostering global policies that align with their principles. This document was the inspiration for the formation of the IEEE P7000 Standards Working Groups, which established a model by which engineers and technologists can address ethical consideration throughout the various stages of system design and creation. The working groups remain open for comments and feedback from engineers to bring to light ethical considerations encountered when designing and implementing a new system.

Next steps toward the development of standards for funders and grantees to identify and mitigate biological risks during research design: In 2019, we propose

[12] National Academies of Sciences, Engineering, and Medicine (2017). Gaps in the International Governance of Dual-Use Research of Concern. Washington, DC: The National Academies Press.
https://sites.nationalacademies.org/cs/groups/pgasite/documents/webpage/pga_176434.pdf
[13] The IEEE Global Initiative on Ethics of Autonomous and Intelligent Systems, retrieved 03 October 2018 from https://ethicsinaction.ieee.org/.

to convene a diverse group of funders, researchers, and additional experts from the life-sciences and other scientific and engineering areas to:

1. Determine existing and emerging technologies that would benefit from a common mechanism to assess emerging biosecurity risks.
2. Investigate potential approaches to creating a dynamic mechanism for funders and researchers to identify new biosecurity risks, facilitate their mitigation, and conduct risk-benefit analyses to justify a project.
3. Explore pathways for funders to adopt a standardized biosecurity risk assessment and management tool[14] for research proposals. Such a tool would combine quantitative and qualitative assessments of known life science research risks based on existing global risk frameworks, such as the 2018 NASEM report on risks posed by synthetic biology[15].
4. Identify a pilot project, in coordination with one or more research funders, to evaluate the feasibility and impact of applying new standards during 2020-2021.

[14] Concept based on the Grant Risk Assessment and Management (GRAM) Tool, developed by the Global Fund (2015). http://www.aidsalliance.org/assets/000/003/097/08._gram_guidelines_implementer_version_august_2015_original.pdf?1507209603.
[15] National Academies of Sciences, Engineering, and Medicine (2018). Biodefense in the Age of Synthetic Biology. Washington, DC: The National Academies Press. https://doi.org/10.17226/24890.