

Novel and Exceptional Technology and Research Advisory Committee

**Draft Report of the Gene Drives
in Biomedical Research
Working Group**

JUNE 2021





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Roster

Chair

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Distinguished Professor
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Loeb Eminent Scholar Chair in Pediatrics
Vice Chair for Research, UAB Pediatrics
Associate Director, Drug Discovery and Development,
Comprehensive Cancer Center
Division of Pediatric Infectious Disease
School of Medicine
University of Alabama at Birmingham
Birmingham, AL 35233

Members

ADELMAN, Zach N., PhD
Professor and Presidential Impact Fellow
Department of Entomology
Texas A&M University
College Station, TX 77843

ALBRITTON, Lorraine M., PhD
Professor Emeritus
Department of Microbiology, Immunology, and
Biochemistry
College of Medicine
The University of Tennessee Health Science Center
Memphis, TN 38163

BLOSS, Cinnamon, PhD
Associate Professor
Herbert Wertheim School of Public Health and
Human Longevity Science
University of California, San Diego
La Jolla, CA 92093

BORIS-LAWRIE, Kathleen, PhD
Professor
Department of Veterinary and Biomedical Sciences
University of Minnesota
Saint Paul, MN 55108

CHO, Mildred, PhD
Professor, Departments of Pediatrics and Medicine
Associate Director
Stanford Center for Biomedical Ethics
Stanford University School of Medicine
Stanford, CA 94305

DZIRASA, Kafui, MD, PhD
Associate Professor of Psychiatry and Behavioral
Sciences
K. Ranga Rama Krishnan Endowed Associate
Professor
Assistant Professor of Biomedical Engineering
Associate Professor in Neurobiology
Assistant Professor in Neurosurgery
Investigator in the Duke Institute for Brain Sciences
Duke University Medical Center
Durham, NC 27710

GRONVALL, Gigi Kwik, PhD
Associate Professor
Department of Environmental Health and Engineering
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD 21202

LEE, Benhur, MD
Professor
Department of Microbiology
Ward-Coleman Chair in Microbiology
Icahn School of Medicine at Mount Sinai
New York, NY 10029

LEE, Dean A., MD, PhD
Professor of Hematology, Oncology and Bone Marrow
Transplantation
DiMarco Family Endowed Chair in Cell Based Therapy
Director, Cellular Therapy and
Cancer Immunology Program
Nationwide Children's Hospital
The Ohio State University
Columbus, OH 43205

LESHNER, Alan I., PhD
Chief Executive Officer, Emeritus
American Association for the Advancement of Science
Potomac, MD 20854

LEWIS-HALL, Freda C., MD, DFAPA
Former Executive Vice President
Pfizer Inc.
New York, NY 10017

MCCARTY, Douglas, PhD
Senior Director, Vector Development
Pfizer Rare Disease Research Unit
Morrisville, NC 27560

OSSORIO, Pilar N., PhD, JD
Professor of Law and Bioethics
University of Wisconsin
Madison, WI 53706

OYE, Kenneth, PhD
Professor, Political Science and Data, Systems and
Society
Director, Program on Emerging Technologies
Center for International Studies
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

PORTEUS, Matthew, MD, PhD
Professor of Pediatrics (Pediatric Stem Cell
Transplantation)
Department of Pediatrics
Stanford Medical School
Stanford University
Stanford, CA 94305

RILEY, Margaret F., JD
Professor, School of Law
Professor of Public Health Science
School of Medicine
Professor of Public Policy
Batten School of Leadership and Public Policy
University of Virginia
Charlottesville VA 22903

THIBOLDEAUX, Kim D.
Chief Executive Officer
Cancer Support Community
Washington, DC 20005

TURNER, Leigh, PhD
Associate Professor
Center for Bioethics
School of Public Health
College of Pharmacy
University of Minnesota
Minneapolis, MN 55455



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Novel and Exceptional Technology and Research Advisory Committee (NExTRAC) Gene Drives in Biomedical Research Working Group

Co-Chairs

ADELMAN, Zach N., PhD
Professor and Presidential Impact Fellow
Department of Entomology
Texas A&M University
College Station, TX 77843

BLOSS, Cinnamon, PhD
Associate Professor
Herbert Wertheim School of Public Health and Human
Longevity Science
University of California, San Diego
La Jolla, CA 92093

Members

BORIS-LAWRIE, Kathleen, PhD
Professor
Department of Veterinary & Biomedical Sciences
University of Minnesota
Saint Paul, MN 55108

LEE, Benhur, MD
Professor, Department of Microbiology
Ward-Coleman Chair in Microbiology
Icahn School of Medicine at Mount Sinai
New York, NY 10029

LEE, Dean A., MD, PhD
Professor of Hematology, Oncology and Bone Marrow
Transplantation
DiMarco Family Endowed Chair in Cell Based Therapy
Director, Cellular Therapy and Cancer Immunology
Program
Nationwide Children's Hospital
The Ohio State University
Columbus, OH 43205

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OYE, Kenneth, PhD
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Society
Director, Program on Emerging Technologies
Center for International Studies
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

PORTEUS, Matthew, MD, PhD
Professor of Pediatrics (Pediatric Stem Cell
Transplantation)
Department of Pediatrics
Stanford Medical School
Stanford University
Stanford, CA 94305

Ad Hoc Members

Collins, James, P., PhD
Virginia M. Ullman Professor of Natural History and the
Environment
School of Life Sciences
Arizona State University
Tempe, AZ 85287

Delborne, Jason, PhD
Professor of Science, Policy, and Society
Department of Forestry and Environmental Resources
Genetic Engineering and Society Center
North Carolina State University
Raleigh, NC 27695

Hall, B. Fenton, MD, PhD
Chief
Parasitology and International Programs Branch
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Rockville, MD 20852

Heitman, Elizabeth, PhD
Professor
Program in Ethics in Science and Medicine
University of Texas Southwestern Center
Dallas, Medical TX 75390

CONTENTS

Executive Summary	1
I. Introduction	4
II. Context and Overview of Report	7
A. Need for Clear Definitions to Promote Common Understanding of Terms	7
B. Organization of Report	8
III. Biosafety Guidance for Contained Research	10
A. Background	10
B. Recommendations	13
IV. Biological and Environmental Risk Mitigation	
Approaches	17
A. Background	17
B. Recommendations	22
V. Strategies for Risk/Benefit Assessments for Field Release of Gene Drive Modified Organisms	25
A. Background	25
B. Recommendations	29
VI. Strategies for Stakeholder Engagement Regarding Gene Drive Modified Organisms	34
A. Background	34
B. Recommendations	39

VII. Conclusions for Biosafety Guidance for Contained Research and Conditions for Field Release of Gene Drive Modified Organisms	43
A. Background	43
B. Overarching Considerations Related to Biosafety Guidance for Contained Research	43
C. Overarching Considerations for Field Release	45
D. Summary	49
APPENDIX 1: Glossary and Acronym Definitions	51
APPENDIX 2: Current Biosafety Guidance for Contained Research	55

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Novel and Exceptional Technology and Research Advisory Committee (NExTRAC)

Gene Drives in Biomedical Research Working Group Draft Report

Executive Summary

Recent advances in gene drive technologies present opportunities for many applications with potential benefits to public health, agriculture, and the environment but also raise safety, ethical, and social concerns, particularly as research progresses towards field release of gene drive modified organisms. To help address issues associated with conducting gene drive research safely and responsibly, the National Institutes of Health (NIH) Director established the Gene Drives in Biomedical Research Working Group of the Novel and Exceptional Technology and Research Advisory Committee (NExTRAC)¹ and presented the following charge to the Working Group:

- Consider whether existing biosafety guidance is adequate for contained laboratory research utilizing gene drive technology
- Outline conditions (if any) under which NIH could consider supporting field release of gene drive modified organisms

During its deliberations, the Working Group reviewed the current state of gene drive technologies and experiences with other technologies involving field release of gene drive modified organisms. They considered the adequacy of existing biosafety guidance and strategies for biological and environmental risk mitigation for both laboratory and field release research, assessing potential harms and potential benefits, and identifying and engaging stakeholders. The Working Group consulted with subject matter experts in these areas including at a public NExTRAC workshop, *Gene Drives: Biosafety Guidance and Conditions for Field Release Research*. Public comments were also considered by the NExTRAC as part of the deliberations on the draft report presented by the Working Group.

The extraordinary ability of gene drives to spread quickly throughout a population creates substantial uncertainty concerning potential benefits and harms. Thus, NIH should ensure it

¹ National Institutes of Health. (n.d.). *Novel and Exceptional Technology and Research Advisory Committee*. U.S. Department of Health and Human Services. <https://osp.od.nih.gov/biotechnology/main-nextrac/>

supports research to address gaps in knowledge and implementation, and has the proper guidance and requirements for research proposals and applications in place to continue to fund contained laboratory research and to consider funding future field release research. The NExTRAC concluded that NIH should cautiously consider funding gene drive research leading up to and/or including potential field release on a case-by-case basis if certain recommendations are met (Table 1). Importantly, any final decision on whether there is approval to release a gene drive modified organism into the field would ultimately be made by regulators and local authorities, which will vary depending on the location of the proposed field release and should be informed by rigorous risk/benefit assessments and stakeholder/community engagement. If NIH funds proposals that have, as part of the research strategy, a plan to conduct eventual field release, such proposals should articulate what the impact of the research will be even if field release ultimately does not occur, whether due to a regulatory decision, the outcomes of the risk/benefit assessment, or other factors.

Table 1. Report Summary Recommendations

Report Section	Recommendations
<p>Biosafety Guidance for Contained Research (pages 10-16)</p>	<ul style="list-style-type: none"> • NIH should develop guidance (or incorporate existing guidance into relevant documents) that (1) includes uniform standards for design and construction of physical containment facilities and considerations for biosafety work practices as appropriate, and (2) anticipates the diversity of species that could be used in gene drive research. • NIH should provide additional guidance (or incorporate existing guidance into relevant documents) on the considerations for risk assessments for laboratory gene drive research to assist investigators, biosafety professionals, and Institutional Biosafety Committees (IBCs) in determining appropriate conditions for contained research (e.g., dealing with complexity, uncertainty, and context). • NIH should require appropriate expertise in the review of gene drive research, namely: <ol style="list-style-type: none"> 1. NIH should develop guidance for institutions to augment the composition of IBCs for review of gene drive research to include members with additional specific expertise (e.g., entomology, ecology, evolutionary biology) as appropriate. 2. NIH should require that a Biological Safety Officer be appointed to the IBC when the institution conducts experiments with gene drive modified organisms capable of spreading in the environment if the organisms were to escape from containment.
<p>Biological and Environmental Risk Mitigation Approaches (pages 17-24)</p>	<ul style="list-style-type: none"> • NIH should support research on biological risk mitigation strategies for gene drive research, including the identification of critical areas of uncertainty and the development of approaches to mitigate those uncertainties. • NIH should require all requests for support of field trials involving gene drive modified organisms to include a Localization Plan (which articulates how the gene drive is proposed to be confined/reversed) in the Approach section of the NIH application or proposal.

	<ul style="list-style-type: none"> • NIH should support research on environmental risk mitigation strategies based on evaluation of the impact of gene drive modified organisms on eco-evolutionary dynamics and informed by input from community representatives and stakeholder engagement.
<p>Strategies for Risk/Benefit Assessments for Field Release of Gene Drive Modified Organisms (pages 25-33)</p>	<ul style="list-style-type: none"> • NIH should require all requests for support of field trials involving gene drive modified organisms to: <ol style="list-style-type: none"> 1. Include a risk/benefit assessment plan in the Approach section of the NIH application or proposal. Such plans should address the assessment of potential benefits and potential harms, and to whom they would accrue, and identify which environments and which aspects of the environments would be affected. 2. Articulate phased research plans with research activities designed to proceed from lower to higher risk in the Approach section of the NIH application or proposal. 3. Define milestones for decisions regarding whether to proceed to the next phase, as part of the Approach section of the NIH application or proposal. 4. Utilize an independent board to provide input on the assessments of potential benefits/harms, milestones, and any associated recommendations for potential field release studies. 5. Make risk/benefit assessments publicly available, as well as any associated recommendations from the independent board, in a timely manner and to the greatest extent allowable by law.
<p>Strategies for Stakeholder Engagement Regarding Gene Drive Modified Organisms (pages 34-42)</p>	<ul style="list-style-type: none"> • NIH should support planning projects to identify potential trial sites and associated stakeholders, as well as establish, organize, or conduct preliminary engagement activities that could inform future trials. • NIH should require all requests for support of field release research involving gene drive modified organisms to include a plan for stakeholder and community engagement in the Approach section of the NIH application or proposal. The plan should articulate who will perform engagement activities, as well as how stakeholder and community input would be incorporated into decisions about experimental design and whether to proceed through the phases of the research plan. • NIH should support research focused on establishing best practices for stakeholder engagement relevant for either laboratory or field-based gene drive research.



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Novel and Exceptional Technology and Research Advisory Committee (NExTRAC)

Gene Drives in Biomedical Research Working Group Draft Report

I. Introduction

The purpose of the NExTRAC, as noted in the Committee’s charter, is to “...provide advice to the Director,[NIH], on matters related to the conduct and oversight of research involving emerging technologies in biomedical science (also referred to as emerging biotechnologies). The Committee will address scientific, safety, ethical, and social issues associated with areas of emerging biotechnology research for which the NIH requests advice or guidance.” To launch the work of the Committee, the NIH Director established the Gene Drives in Biomedical Research Working Group, providing the following charge to the NExTRAC:

- “Consider whether existing biosafety guidance is adequate for contained laboratory research utilizing gene drive technology
- Outline conditions (if any) under which NIH could consider supporting field release of gene drive modified organisms

Provide advice on the following issues:

- Given the diverse applications and species that may be used in gene drive research with different risks, is the current landscape of biosafety guidance adequate for contained research?
- What knowledge and conditions should be in place to help ensure that field release research of gene drive modified organisms could be conducted safely and ethically?”

Gene drive technology is an emerging technology with many applications that present both exciting opportunities and challenging issues. Gene drives have the capacity to spread engineered traits through a population at a rate much faster than is possible by normal Mendelian inheritance. While engineered gene drive has existed since the early 1990s, this technology has advanced recently with the development of highly precise gene editing tools, like Clustered Regularly-Interspaced Short Palindromic Repeats (CRISPR)/Cas9, which allow for easier and more precise introduction of the gene drive system and targeting of the desired trait.

NIH supports basic gene drive research for its potential to benefit public health, such as by altering the mosquito genome to reduce transmission of vector-borne human diseases, like malaria, dengue, or Zika. Gene drive technologies may also be pursued for applications beyond public health, such as control of invasive species; such potential applications are not the focus of the charge to the Committee, though the Committee notes that much of the context and recommendations could be relevant for other applications. Despite the important potential public health benefits afforded by gene drive technologies, there are also significant concerns about potential ecological consequences, which may or may not be predictable, and concerns regarding ethical and social issues associated with gene drive technologies. These concerns arise because the release of gene drive modified organisms into the environment could have irreversible or unpredictable ecological impacts. In the context of this report, gene drive research includes the entire spectrum of research necessary for eventual practical applications, including basic laboratory research, the conduct of risk assessments for contained research, research to develop and understand the effectiveness of risk management and mitigation strategies, approaches to conducting assessments of the impacts (both potential benefits and potential harms) of releasing gene drive modified organisms, stakeholder engagement, and ultimately (if pursued), actual release of gene drive modified organisms into the environment.

Currently, NIH-supported research is focused on developing gene drive technologies and safeguards, models of spread, and applications for basic science or public health studies in organisms, including several species of mosquitos, *Caenorhabditis elegans*, and rodents. NIH also supports related research with organisms such as the bacterium *Wolbachia* or the entomopathogenic fungus *Metarhizium*. NIH does not currently support studies involving field release of gene drive modified organisms.

To enhance the responsible development of these technologies, NIH provided support for the 2016 National Academies of Science, Engineering, and Medicine (NASEM) study, *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*² (which will be referred to as the 2016 NASEM report throughout this document). NIH accepted the report's recommendations that basic and applied research into gene drives should continue to be supported, but studies involving release of gene drive modified organisms into the environment should not be supported at that time. As gene drive research continues to advance toward field release studies, this is an opportune time to revisit the issue of whether to proceed with this research and, if so, how to do so safely and ethically. Such decisions must be made with the recognition that regulators and local/national authorities and communities will ultimately decide whether they give permission to proceed with field release, and both US-

² National Academies of Sciences, Engineering, and Medicine. (2016). *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*. National Academies Press. <https://doi.org/10.17226/23405>

based regulations and international treaties will inform these decisions. NIH, however, has a responsibility to carefully consider whether, and (if so) how, to fund such research responsibly.

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II. Context and Overview of Report

The charge to the Committee was broken into two parts – one focused on the safe conduct of contained research with gene drive modified organisms (that is, the organisms remain physically contained and are not intended to be released into the environment); and the other on field release research (that is, research that involves the deliberate introduction of a gene drive modified organism into the environment outside of physical containment). A challenge to the organization of this report was that key concepts and themes about gene drive research apply to both contained and field release research. For example, biological risk mitigation strategies such as split gene drive systems and reversal drives could be used to mitigate risks of accidental release from a contained research setting or could be used as a strategy to limit the dissemination of gene drives in a controlled field release research study. Furthermore, transparency and engagement with members of the public and potentially impacted communities are relevant across the research and development landscape, from contained research, to field release research, to broad dissemination of gene drives. Additionally, terms commonly used in the context of gene drive research have different meanings to different audiences; for example, the use of the terms “containment” and “confinement” have been used in gene drive discussions to convey different nuances, and certain professional communities, such as biosafety professionals and ecologists, have their own understanding of the meaning of terms such as “biological containment.”

A. Need for Clear Definitions to Promote Common Understanding of Terms

Key terms will be used throughout the report, and for ease of reading, some of those are outlined here. As noted above, contained research is defined as research that is not intended to be conducted outside of physical containment. Physical containment is a combination of equipment, facilities, and practices, that prevent such release into the outside environment. Biological risk mitigation strategies involve the use of highly specific biological barriers chosen or constructed to limit the transmission, dissemination, or propagation of a gene drive transgene, or the survival of a gene drive modified organism, in the environment. Such strategies can be used in contained research settings (when utilized as such, they can be referred to as biological containment, a familiar term to biosafety professionals) or in field release research to limit the dissemination or propagation of gene drive modified organisms outside the intended targeted area. Environmental risk mitigation strategies are those approaches that use geographically or genetically isolated sites to help prevent spread into non-targeted populations (such as isolated islands or remote locations).

For the purposes of contained research, this report will use the term risk assessment when discussing the review and analysis of ways to assess, manage and mitigate potential risks posed by conducting laboratory research with gene drive modified organisms, such as impacts on the environment due to escape from containment. As discussed above, gene drive

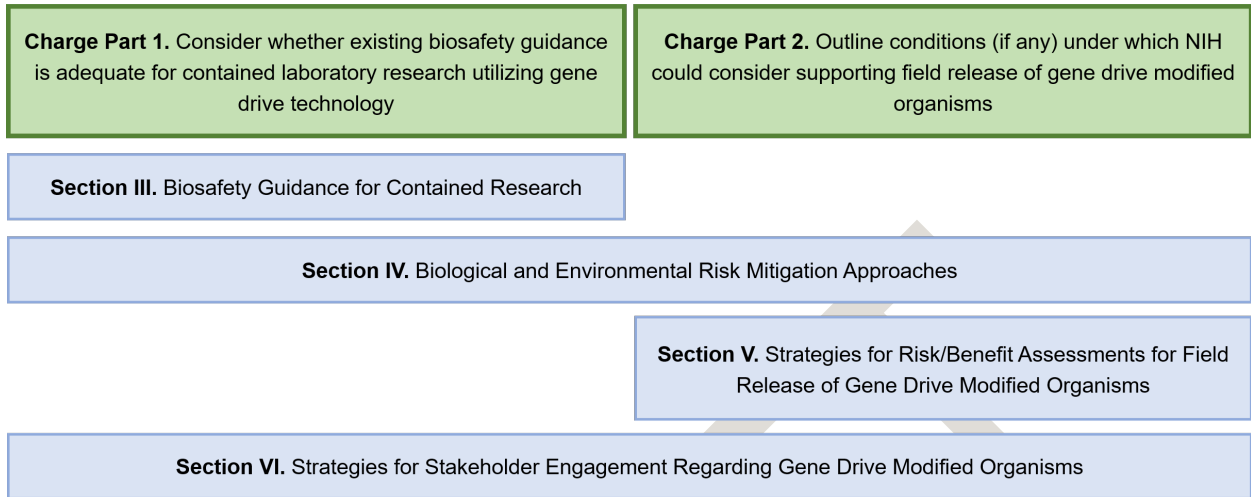
technologies have the potential to yield not only benefits (e.g., for public health) but also harms (e.g., negative environmental consequences). For research involving the field release of gene drive modified organisms, it will be important to consider and weigh all potential impacts, including both potential harms and potential benefits. Thus, in the context of field release research, such an analysis will be referred to as a risk/benefit assessment when deliberating/weighing whether to proceed with a field release.

These key terms and others are included in a glossary in Appendix 1.

B. Organization of Report (Figure 1)

The Committee addressed the portion of the charge focused on “consider[ing] whether existing biosafety guidance is adequate for contained laboratory research utilizing gene drive technology” in Section III. As noted previously, certain concepts, in particular “biological risk mitigation” or “biological containment” span both contained research (Section III) and other sections of the report focused on field release research. Most notably, Section IV addresses biological risk mitigation strategies (which could be used for contained research settings or field release research) and environmental risk mitigation strategies. Section IV is thus crucial to understand the scientific issues that must be addressed relevant to risk mitigation strategies, both for contained research studies and for potential field release research. Section IV and onward can be considered the start of the second portion of the charge to the Committee, to “outline conditions (if any) under which NIH could consider supporting field release of gene drive modified organisms.” Section V reviews strategies for assessing potential harms and potential benefits for gene drive field release research; though there may be some overlap between risk assessments for contained research (addressed in Section III) and for field release research, intentional release of gene drive modified organisms outside of containment poses unique risks that are the focus of Section V. Section VI is focused on strategies for stakeholder engagement regarding gene drive modified organisms. Finally, Section VII outlines the overarching conclusions of the report both in terms of the need for biosafety guidance for contained research, and the conditions for research involving the field release of gene drive modified organisms, should NIH decide to support such studies.

Figure 1. Organization of Report



III. Biosafety Guidance for Contained Research

A. Background

The first part of the Committee’s charge was to “consider whether existing biosafety guidance is adequate for contained laboratory research utilizing gene drive technology.” The Committee considered the adequacy of existing biosafety guidance for contained research (i.e., research conducted with gene drive modified organisms that are not intended to be released into the environment) and the needs of the research community in order to formulate recommendations for consideration by NIH. One recent survey of biosafety professionals suggested that additional guidance for contained research with gene drive modified organisms would be welcomed by the research and biosafety communities.³ Gene drive approaches, unlike most biological research, may ultimately be effective precisely because they are not easily contained; therefore, they pose some unique challenges in applying existing biosafety guidance.

The Committee identified four primary guidance documents in the U.S. that articulate biosafety principles and oversight requirements that are applicable to gene drive research: the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*,⁴ *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*,⁵ the *Arthropod Containment Guidelines (ACG)*,⁶ and the United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) *Plant Protection and Quarantine (PPQ) Containment Guidelines for Nonindigenous Phytophagous Arthropods and Their Parasitoids and Predators (2002)*.⁷ Internationally, the *World Health Organization (WHO) Laboratory Biosafety Manual* (4th edition) outlines best practices in biosafety.⁸ See Table 3 in Appendix 2 for a description of these and other relevant biosafety guidance documents for contained research.

These biosafety guidance documents are built on a foundational need for comprehensive risk assessment to determine appropriate equipment, containment facilities, and practices and procedures for the safe handling of biological materials. These documents include detailed

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- ³ O’Brochta, D. A., Tonui, W. K., Dass, B., & James, S. (2020). A Cross-Sectional Survey of Biosafety Professionals Regarding Genetically Modified Insects. *Applied Biosafety*, 25(1), 19–27. <https://doi.org/10.1177/1535676019888047>
- ⁴ U.S. National Institutes of Health. (2019). *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*. U.S. Department of Health and Human Services. https://osp.od.nih.gov/wp-content/uploads/2019_NIH_Guidelines.htm
- ⁵ Centers for Disease Control and Prevention. (2020). *Biosafety in Microbiological and Biomedical Laboratories: 6th Edition*. U.S. Department of Health and Human Services. <https://www.cdc.gov/labs/pdf/CDC-BiosafetyMicrobiologicalBiomedicalLaboratories-2020-P.pdf>
- ⁶ American Committee of Medical Entom. (2019). *Arthropod Containment Guidelines*, Version 3.2. *Vector-Borne and Zoonotic Diseases*, 19(3), 152–173. <https://doi.org/10.1089/vbz.2018.2431>
- ⁷ Animal and Plant Health Inspection Service. (2002). *Containment Guidelines for Nonindigenous, Phytophagous Arthropods and their Parasitoids and Predators*. U.S. Department of Agriculture. https://www.aphis.usda.gov/plant_health/permits/downloads/arthropod_biocontrol_containment_guidelines.pdf
- ⁸ World Health Organization. (2020). *Laboratory biosafety manual, fourth edition and associated monographs*. License: [CC BY-NC-SA 3.0 IGO](https://creativecommons.org/licenses/by-nc-sa/3.0/). <https://www.who.int/publications/i/item/9789240011311>

guidance on physical containment (such as descriptions of biosafety levels and risk groups for human etiologic agents), as well as information on biological containment and the process of conducting a risk assessment.

i. Physical Containment

The objective of physical containment is to confine organisms and to reduce the potential for exposure of laboratory workers and people outside of the laboratory, as well as to prevent escape into the environment. Physical containment is achieved through a combination of special laboratory design, containment equipment, and biosafety practices and procedures appropriate for the operations being performed. The primary means of physical containment is provided by containment equipment. The design and construction of the laboratory facility provide a secondary means of protection against the escape of organisms outside the laboratory or to the environment. Specific facility practices and procedures add additional levels of biosafety control.

The four biosafety levels (BL or BSL) described in the *NIH Guidelines* and the *BMBL* are applicable to standard microbiological or biomedical laboratory settings. In such settings, BL1 is appropriate for research that poses very low risk to human health or the environment. BL4 involves the use of highly stringent containment conditions and is used to conduct research with biological agents that pose high risk to individual and community health. These standard biosafety levels may not be directly applicable to research with gene drive modified organisms.

Particularly relevant to gene drive research, which frequently involves using arthropods, is the *ACG*, which describes four Arthropod Containment Levels (ACL). Currently, ACL2 is recommended for any type of genetically modified arthropod, but gene drive modified insects may require additional containment measures in some cases.⁹

ii. Biological Containment

Since the advent of recombinant DNA technologies, comprehensive approaches to risk mitigation have complemented physical containment with biological methods. Biological containment involves employing specific biological barriers such as those that limit survival, propagation, etc. in the environment outside of a contained research setting. Such biological strategies are discussed further in Section IV.

Biological containment methods can be used in research with gene drive modified organisms to mitigate potential risks posed by an inadvertent laboratory escape. Such methods could also

⁹ Benedict, M. Q., Burt, A., Capurro, M. L., De Barro, P., Handler, A. M., Hayes, K. R., Marshall, J. M., Tabachnick, W. J., & Adelman, Z. N. (2018). Recommendations for Laboratory Containment and Management of Gene Drive Systems in Arthropods. *Vector-Borne and Zoonotic Diseases*, 18(1), 2–13. <https://doi.org/10.1089/vbz.2017.2121>

ultimately be used to mitigate risks when conducting research involving intentional field release of gene drive modified organisms.

iii. Summary of Physical and Biological Containment Approaches

While this combined approach of physical containment and biological containment has been applied successfully to laboratory research involving recombinant DNA modified organisms for over forty years, to date, research has focused on a limited number of model organisms, with modifications reducing the fitness of animals already weakened by adaptation to the laboratory. The pace at which gene editing and genome modification technologies are being applied to new organisms is accelerating, and this is compounded by gene drive technologies that present even greater challenges for existing physical and biological containment approaches. Gene drive systems, for example, may not be limited by the loss of fitness often associated with introduction of transgenes, as they are designed to spread despite any associated fitness disadvantage as compared to wild type organisms.

iv. Risk Assessments for Gene Drive Research in Contained Laboratory Settings

The *NIH Guidelines* involve a tiered system of review, with more oversight required for higher risk experiments. In addition, the *NIH Guidelines* define the responsibilities of the Institutional Biosafety Committee (IBC), which is the institutional body responsible for reviewing research subject to the *NIH Guidelines*. Some gene drive work that has been performed to date would fall into the category that requires IBC review and approval before the research can begin. However, gene drive work performed in rodents, baker's yeast, or non-invasive plant species may fall into other categories that render the research either exempt from review or place it in a category where review is not required until after work has been initiated.

In the *NIH Guidelines*, risk assessments for contained research focus primarily on assigning a risk group (RG) to an agent and setting containment levels for safe handling based on the manipulations to the agent being performed. While RGs defined for etiologic agents do not apply to gene drive containing organisms, the concept of assigning a risk category may have utility in risk assessments for gene drive research.¹⁰

v. Scope and Applicability of Existing U.S. Biosafety Guidance

The existing U.S. guidance documents do not specifically address biosafety for gene drive research in contained laboratory settings. The *NIH Guidelines* cover the generation of transgenic organisms, including animals and plants and administration of recombinant or synthetic nucleic acid molecules to animals and plants, and provide relevant risk assessment and physical containment approaches suitable for microbiological applications, large animals,

¹⁰ Adelman, Z. N. (2021). Demystifying the Risk Assessment Process for Laboratory-Based Experiments Utilizing Invasive Genetic Elements: It Is More Than Gene Drive. *Applied Biosafety*. <https://doi.org/10.1089/apb.20.0074>

and plants. Similarly, the *BMBL* addresses risk assessment and physical containment as risk mitigation methods, including minimizing environmental release. However, neither of these documents specify appropriate containment conditions for small, rapidly reproducing organisms such as arthropods. The *ACG* includes a description of ACLs to contain arthropods that are infectious disease vectors, but the appropriate ACL is largely based on the pathogen the vector is infected with, not the arthropod itself. Moreover, adoption of the *ACG* is primarily limited to the subdiscipline of vector biology. Similarly, the *USDA APHIS PPQ Containment Guidelines* provide physical containment recommendations for the safe handling and manipulation of arthropods but are utilized only when moving arthropods that are either exotic or modified to contain plant pest sequences across state lines.

Of the four documents, only the *NIH Guidelines* are required to be followed when conducting certain research (namely, research that is conducted at or sponsored by an institution that receives any support for recombinant or synthetic nucleic acid research from NIH). However, not all institutions that may conduct gene drive research are subject to the *NIH Guidelines*. The other documents are intended as references for best practices, or as a condition of a specific federal permit.

B. Recommendations (Figure 2)

Based on the assessment conducted by the Committee, the NEXTRAC has provided recommendations for NIH to consider in developing additional biosafety guidance regarding physical and biological containment of gene drive modified organisms and to advise on the components of effective risk assessment for contained research. Additionally, NIH should take steps to require the inclusion of relevant experts in the review of contained gene drive experiments.

3.1 NIH should develop guidance (or incorporate existing guidance into relevant documents) that (1) includes uniform standards for design and construction of physical containment facilities and considerations for biosafety work practices as appropriate, and (2) anticipates the diversity of species that could be used in gene drive research.

There is a need for unified physical biosafety guidance for contained laboratory research with arthropods or similar fast reproducing organisms where invasive transgenes such as gene drives capable of spreading in the environment could be developed. While the general principles of physical containment described in existing documents specific to research with arthropods are useful, containment facilities and associated work practices, particularly for arthropods across disciplines, are not uniform and are very dependent on their interpretation and adoption by individual investigators and institutions. Specific guidance provided by NIH would standardize biosafety performance across institutions.

Additionally, although extensive guidance on physical containment principles exists for species commonly used in biomedical research (e.g., rodents) and for arthropods, there is also a need to ensure that appropriate guidance is available for a range of other species likely to be used in gene drive research in the future (e.g. fish, plants). Guidance is also needed for biological containment.

3.2 NIH should provide additional guidance (or incorporate existing guidance into relevant documents) on the considerations for risk assessments for laboratory gene drive research to assist investigators, biosafety professionals, and IBCs in determining appropriate conditions for contained research (e.g., dealing with complexity, uncertainty, and context).

The *NIH Guidelines* recommend stepwise higher levels of containment in the presence of pathogens, recombinant or synthetic nucleic acid molecules derived from pathogens, or toxins. For recombinant or synthetic nucleic acid molecule manipulations in plants, the invasiveness of the recipient species is also explicitly noted as a factor in determining risk. However, current guidance does not mention or consider the presence of recombinant or synthetic nucleic acid molecules that have the potential to spread and persist in the environment as presenting different or increased risks as compared to manipulations unlikely to do so. Thus, it was not surprising that in a 2019 survey of biosafety professionals, only 16% of the respondents thought existing guidance was adequate when considering risk and containment of gene drive modified insects.¹¹ Although the risk mitigation strategies employed in contained settings are likely not very different for organisms modified to contain gene drive transgenes than for other traditional biohazards, there is concern that adequate data may be lacking in some instances to answer key questions for the conduct of a robust risk assessment. Guidance for gene drive risk assessments might include:

- a) Risk category recommendations for specific types of manipulations based on:
 - Function or intended function of the genetic/gene drive construct (i.e., a designed or engineered assembly of sequences)
 - Source of the genetic material (e.g., sequences of transgenes) in the construct
 - The modifications to the construct
 - Whether it is possible to predict the consequences of a construct, including the recognition of an unintended gene drive (i.e., construct not specifically designed as a gene drive but nonetheless having properties of a gene drive) and the possible consequences of escape into the environment
 - The potential ability of the gene drive to spread or persist in local populations

¹¹ O'Brochta, D. A., Tonui, W. K., Dass, B., & James, S. (2020). A Cross-Sectional Survey of Biosafety Professionals Regarding Genetically Modified Insects. *Applied Biosafety*, 25(1), 19–27. <https://doi.org/10.1177/1535676019888047>

- b) The types of scientific questions that need to be answered and what data are needed to facilitate the risk assessment
- c) Options for approaches to risk mitigation for specific risk categories of experiments or when dealing with a high degree of uncertainty about risks
- d) When to consider implementation of more stringent containment measures until biosafety data are accrued to support lowering containment

3.3 NIH should require appropriate expertise in the review of gene drive research, namely:

3.3.1 NIH should develop guidance for institutions to augment the composition of IBCs for review of gene drive research to include members with additional specific expertise (e.g., entomology, ecology, evolutionary biology) as appropriate.

3.3.2 NIH should require that a Biological Safety Officer (BSO) be appointed to the IBC when the institution conducts experiments with gene drive modified organisms capable of spreading in the environment if the organism were to escape from containment.

Under the *NIH Guidelines*, research is overseen at the local level by the IBC. IBC members should collectively have the appropriate scientific expertise to be able to review the risks of the research conducted at the institution and should have a broad understanding of principles of biosafety and physical and biological containment. However, with respect to conducting risk assessments for gene drive research, IBCs may need a broader array of expertise compared to the review of research with pathogens or other biomedical research.

The *NIH Guidelines* require IBCs to have the necessary expertise to review relevant experiments under their purview. However, due to the relatively recent development of gene drive technologies, the assessment of potential risks to the environment posed by the escape of gene drive modified organisms is an aspect not typically undertaken by IBCs. While institutions with entomology research programs are likely able to include individuals with expertise on arthropod containment on their IBCs, committees at many institutions may not include members with experience and/or competence in ecological or environmental impact assessment. NIH should develop guidance to institutions to clarify that, when IBCs review contained gene drive research, they should include individuals with relevant expertise to assess risks that may be posed to the environment by the organism used in the research as well as other risks that may be present.

Additionally, the *NIH Guidelines* currently require appointment of a BSO to the IBC if the institution is performing specific types of activities (such as research in high containment

facilities or research involving more than 10 liters of culture). In the *NIH Guidelines*, a key function of the BSO is to conduct periodic facility inspections. Inspections of facilities housing gene drive modified organisms are also critical to ensure that containment standards are rigorously followed. Appointment of a BSO is not currently required for gene drive research, and, given some of the unknown risks associated with such research, an increased level of oversight through the appointment of a BSO for such research is recommended.

By adopting the above recommendations, NIH can help to provide additional clarity and guidance for appropriate biosafety considerations for contained research in this evolving field of science. Appropriate biosafety practices for gene drive research using physical or biological containment are crucial to allow for further responsible advancement of these technologies.

Figure 2. Recommendations for Biosafety Guidance for Contained Research



IV. Biological and Environmental Risk Mitigation Approaches

A. Background

Effective biological and environmental risk mitigation strategies can contribute to the safe and responsible conduct of gene drive research. Since the advent of recombinant DNA technologies, comprehensive approaches to biological containment have complemented physical containment. Biological risk mitigation strategies employ the use of highly specific biological barriers that may be either natural or genetically modified biological characteristics of the organism. In the case of gene drive modified organisms, the risk of escape from the laboratory or of unintended impacts of field release could be decreased by using such barriers to limit the transmission, propagation, and survival of an organism modified to contain an otherwise invasive gene drive transgene.

Environmental risk mitigation strategies use physically or genetically isolated sites (e.g., remote islands) or selection of an environment inhospitable to the gene drive modified organism to help prevent the spread of any gene drive transgenes into non-targeted populations. These strategies can be employed to limit adverse effects in the event of escape from a contained laboratory setting as well as those posed by intentional field release of gene drive modified organisms. As such, biological and environmental risk mitigation approaches – either alone or in combination – are applicable both to contained research (in combination with physical containment) and in field release studies.

While this combination approach has been applied successfully to research involving recombinant or synthetic nucleic acid molecules historically, gene drive technologies may present greater challenges for risk mitigation. Gene drive systems may not be limited by a loss of fitness that is often associated with the introduction of transgenes to an organism that might reproduce with a wild-type population. In fact, gene drive transgenes may be preferentially inherited despite any associated fitness disadvantage as compared to wild type organisms.

i. Biological Risk Mitigation

Different biological risk mitigation strategies for gene drive modified organisms are being developed. These strategies vary depending on the features of the gene drive technology that determine whether the gene drive modified organism is intended to spread and persist in the environment. More detailed descriptions of types of gene drive are provided in Table 2. Non-localized approaches can be designed to spread through a population and persist (e.g.,

modification drive) or cause the population to decrease (e.g., suppression drive).^{12,13} For example, some gene drive technologies target a sequence that is highly or absolutely conserved in all individuals of a particular species and thus could be capable of spreading throughout a population. A major challenge of such potential non-localized approaches is that the footprint of the impacted area (including communities and affected ecosystems) is sufficiently large that the risk/benefit assessment process, ability to engage communities, and potential to reverse effects all become exceedingly difficult to manage. The use of risk mitigation strategies to provide some degree of localization could potentially reduce the complexity associated with these processes.

Depending on the species of gene drive modified organisms, conventional (non-genetic) control measures, such as toxicants or insecticides, could be used to eliminate the gene drive carrying population. These methods would have the same limitations associated with their use to control the non-modified population of the organism, and the risks associated with their use need to be considered. Nonetheless, such conventional control measures could serve as an important backstop to limit potential negative impacts of field release in some instances. “Reversal drives” or other neutralizing genetic elements have also been proposed as a strategy to remove gene drive transgenes from the environment.¹⁴ However, concerns have been raised about reliance on introducing additional gene drive modified organisms to mitigate against any unintended consequences of the release of an initial gene drive, in part because such approaches may be unlikely to be widely supported by communities that may be impacted by such consequences.¹⁵

Localized gene drive approaches are those that are designed to spread only in a temporally or spatially defined region. In essence, such localized approaches hinge on the notion that the design of the gene drive itself serves as a biological risk mitigation strategy. These approaches may also be referred to as “self-limiting drives,” but “localized” is the term used in this report. One type of localization approach is a high threshold gene drive. High threshold drives, such as translocations or underdominance systems, require release of organisms above a threshold to be able to spread to fixation; release of fewer organisms would result in the introduced trait disappearing from the population after a few generations. Other localization approaches include split homing drives, which separate the Cas9 nuclease from the guide RNAs at different loci on chromosomes or lines of organisms that would need to be crossed; these strategies help

¹² Adolphi, A., Gantz, V. M., Jasinskiene, N., Lee, H.-F., Hwang, K., Terradas, G., Bulger, E. A., Ramaiah, A., Bennett, J. B., Emerson, J. J., Marshall, J. M., Bier, E., & James, A. A. (2020). Efficient population modification gene-drive rescue system in the malaria mosquito *Anopheles stephensi*. *Nature Communications*, 11(1). <https://doi.org/10.1038/s41467-020-19426-0>

¹³ Holman, L. (2019). Evolutionary simulations of Z-linked suppression gene drives. *Proceedings of the Royal Society B: Biological Sciences*, 286(1912), 20191070. <https://doi.org/10.1098/rspb.2019.1070>

¹⁴ Xu, X.-R. S., Bulger, E. A., Gantz, V. M., Klansseck, C., Heimler, S. R., Auradkar, A., Bennett, J. B., Miller, L. A., Leahy, S., Juste, S. S., Buchman, A., Akbari, O. S., Marshall, J. M., & Bier, E. (2020). Active Genetic Neutralizing Elements for Halting or Deleting Gene Drives. *Molecular Cell*, 80(2), 246-262.e4. <https://doi.org/10.1016/j.molcel.2020.09.003>

¹⁵ National Academies of Sciences, Engineering, and Medicine. (2016). Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. *National Academies Press*. <https://doi.org/10.17226/23405>

prevent persistence or spread beyond the release site. Different split homing drives have been demonstrated to function in several species (*Drosophila* sp., mice, yeast, multiple mosquito species). Recently, approaches for self-eliminating gene drive technologies have been modeled.¹⁶ Other approaches establish target sites that are only present in a genetically isolated subpopulation (private allele) or those that are only fixed (locally fixed allele) in such isolated subpopulations or a synthetic allele introduced into a laboratory population for contained studies.¹⁷

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¹⁶ Zapletal, J., Najmitabrizi, N., Erraguntla, M., Lawley, M. A., Myles, K. M., & Adelman, Z. N. (2020). Making gene drive biodegradable. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 376(1818), 20190804. <https://doi.org/10.1098/rstb.2019.0804>

¹⁷ Sudweeks, J., Hollingsworth, B., Blondel, D. V., Campbell, K. J., Dhole, S., Eisemann, J. D., Edwards, O., Godwin, J., Howald, G. R., Oh, K. P., Piaggio, A. J., Prowse, T. A. A., Ross, J. V., Saah, J. R., Shiels, A. B., Thomas, P. Q., Threadgill, D. W., Vella, M. R., Gould, F., & Lloyd, A. L. (2019). Locally Fixed Alleles: A method to localize gene drive to island populations. *Scientific Reports*, 9(1). <https://doi.org/10.1038/s41598-019-51994-0>

Table 2. Current Examples of Types of Gene Drives^{18, 19, 20, 21}

Type	Examples	Proposed Strategy
Non-Localized Gene Drives (Low Threshold, Self-Sustaining)	MEDEA	Maternal toxin targeting an essential gene linked to an embryonic toxin-resistant copy of the essential gene.
	Homing	Typically CRISPR-based with linkage between the nuclease and beneficial effector or targeting a recessive essential gene required for female viability or fertility; nuclease activity targets the allelic position with respects to the gene encoding it.
	CleaveR [Cleave and Rescue (ClvR)]	Typically CRISPR-based cleavage of an essential gene (toxin) while providing a cleavage-resistant copy of targeted essential gene.
	Y-drive systems/ X-shredder	CRISPR-based integrated on Y chromosome, in which redundant X linked sequences are targeted during spermatogenesis, resulting in removal of X-bearing sperm.
Localized Gene Drives	Translocations (High Threshold)	Endonuclease-initiated cleavage of transgenes positioned on nonhomologous chromosomes resulting in homology-directed repair and generation of marked translocations.
	Underdominance Systems (High Threshold)	Maternal-effect lethal underdominance (UD ^{MEL}) system consisting of inversely positioned maternal toxins targeting essential genes linked to embryonic toxin-resistant copies of the essential genes.
	Split Homing (Transient Self-Limiting)	CRISPR-based in which the endonuclease is not linked to its target site.
	Daisy Chain (Transient Self-Limiting)	Local CRISPR-based split drive in which three or more drive components are not linked but interdependent.
	Homing-Targeted Private Allele	Use of nuclease target sites that are present only in a genetically isolated subpopulation (private allele) or those that are fixed only (locally fixed allele) in such isolated subpopulations.

¹⁸ Raban, R. R., Marshall, J. M., & Akbari, O. S. (2020). Progress towards engineering gene drives for population control. *Journal of Experimental Biology*, 223(Suppl_1). <https://doi.org/10.1242/jeb.208181>

¹⁹ Zapletal, J., Najmitabrizi, N., Erraguntla, M., Lawley, M. A., Myles, K. M., & Adelman, Z. N. (2020). Making gene drive biodegradable. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 376(1818), 20190804. <https://doi.org/10.1098/rstb.2019.0804>

²⁰ Greenbaum, G., Feldman, M. W., Rosenberg, N. A., & Kim, J. (2021). Designing gene drives to limit spillover to non-target populations. *PLOS Genetics*, 17(2), e1009278. <https://doi.org/10.1371/journal.pgen.1009278>

²¹ Champer, J., Buchman, A., & Akbari, O. S. (2016). Cheating evolution: engineering gene drives to manipulate the fate of wild populations. *Nature Reviews Genetics*, 17(3), 146–159. <https://doi.org/10.1038/nrg.2015.34>

ii. Environmental Risk Mitigation

Environmental risk mitigation is based on conducting studies at ecologically or genetically isolated locations to help prevent spread into non-targeted populations. For example, studies could be conducted in environments in which the gene drive modified organisms could not survive or reproduce (e.g., tropical organisms studied in an arctic environment, use of non-native organisms that would lack mates in the local environment). Ecologically and genetically isolated sites, such as islands, have been proposed as initial sites for field releases, but much study would be needed into target and other populations, and into the potential for spread to other areas via aircraft, ships, winds, or currents.²² In addition, proposals to conduct the first field releases of gene drive modified organisms on islands may be subject to criticism that such plans are complicit in historical injustices that have viewed islands and their residents as dispensable and so can be subjected to the risks associated with experimentation.²³

iii. Summary of Biological and Environmental Risk Mitigation Approaches

The development of a wide range of effective strategies for biological and environmental risk mitigation will be critical when planning or evaluating any potential field release of gene drive modified organisms. Different combinations of these strategies may be applied as most appropriate for specific gene drive approaches, applications, organisms, conditions of release, environments, and social contexts, and should be informed by stakeholder/community engagement in many instances. However, the diversity and complexity of technologies, organisms, and environments presents a challenge for establishing definitive criteria independent of context.

Fundamentally, there are many gaps in knowledge about risk mitigation approaches for gene drive research. The approaches themselves are experimentally novel and thus uncertainty regarding their effectiveness will remain until sufficient data can be accumulated, a potential circular problem in the case of approaches that can only be tested in the context of an active gene drive. While some approaches have experimental support in small laboratory experiments, many of the studies noted above are still in the modeling phase of research. Nonetheless, the very attributes that could make gene drive technologies most transformative as a means to control intractable public health problems (i.e., their rapid spread through populations) may be more limited when using localized approaches, so the effectiveness of these localized approaches must be considered against other alternatives.

²² Godwin, J., Serr, M., Barnhill-Dilling, S. K., Blondel, D. V., Brown, P. R., Campbell, K., Delborne, J., Lloyd, A. L., Oh, K. P., Prowse, T. A. A., Saah, R., & Thomas, P. (2019). Rodent gene drives for conservation: opportunities and data needs. *Proceedings of the Royal Society B: Biological Sciences*, 286(1914), 20191606. <https://doi.org/10.1098/rspb.2019.1606>

²³ Taitingfong. (2019). Islands as Laboratories: Indigenous Knowledge and Gene Drives in the Pacific. *Human Biology*, 91(3), 179. <https://doi.org/10.13110/humanbiology.91.3.01>

B. Recommendations (Figure 3)

In addition to continuing to provide support for the responsible development of gene drive technologies themselves, NIH should simultaneously support research into risk mitigation strategies that can be used to reduce risk profiles during laboratory or field-based research studies. As noted above, in some cases, risk mitigation strategies are built directly into the gene drive transgenes, so research into gene drive and biological risk mitigation strategies are closely linked and may be difficult or impossible to separate in some instances. Nonetheless, to avoid bias or the appearance of bias, it may be useful for risk mitigation research to be conducted separately from the development of the gene drive technology, when possible. Additionally, NIH should require Localization Plans in requests for support of field trials involving gene drive modified organisms.

4.1 NIH should support research on biological risk mitigation strategies for gene drive research, including the identification of critical areas of uncertainty and the development of approaches to mitigate those uncertainties.

Many biological risk mitigation strategies are at the theoretical or early proof-of-concept stages and require additional research to provide evidence of effectiveness before use as potential safeguards in both laboratory and field release studies. However, it can be challenging to evaluate approaches for risk mitigation strategies separately from studies focused on the development of the gene drive technology, especially in the case of some biological risk mitigation approaches that are part of the gene drive technology. Consideration should be given to whether such risk mitigation research should be conducted separately from the studies focused on the development of the gene drive technology itself (when possible). NIH should support research designed to generate data regarding the effectiveness of particular risk mitigation strategies; additionally, the effectiveness of the risk mitigation approach should be established in a contained research setting prior to any field release. Such research should involve engagement with varied stakeholders on development of credible, relevant, and scientifically appropriate approaches to testing and evaluation. NIH should consider the development of risk mitigation strategies to be as important, if not more important, as the development of the gene drive technologies themselves.

4.2 NIH should require all requests for support of field trials involving gene drive modified organisms to include a Localization Plan (which articulates how the gene drive is proposed to be confined/reversed) in the Approach section of the NIH application or proposal.

As with many other emerging technologies, given the rapid advancement of gene drive research, it is difficult to recommend specific technologies to pursue as being most likely to be safe and effective. However, experimental designs that are confinable and/or

reversible should exhibit a more clearly defined risk profile than approaches with the potential to spread more widely. As gene drive research proceeds from laboratory to field trial sites, NIH should prioritize support for localized gene drive approaches.

Important aspects of a Localization Plan will include, but are not limited to:

- a) The molecular architecture of the gene drive construct (whether it is designed to be confinable; split, high-threshold, targeted to private allele).
- b) Environmental factors such as the levels of gene flow between the target population and neighboring populations, as well as the ability of the organism to survive and persist in the local climate.
- c) The availability, feasibility, and safety of non-gene drive methods (e.g., insecticides) for post-release mitigation.
- d) The effectiveness of any risk mitigation approaches as demonstrated in prior contained laboratory studies.

Support should be provided only to those applications or proposals whose Localization Plans are found to be acceptable by NIH or its designee.

The existence of proven non-genetic methods of mitigation should also be considered when establishing conditions for laboratory experiments or field release. For example, pesticide susceptibility can be leveraged to limit the ability of gene drive modified organisms to spread outside predefined boundaries (i.e., laboratory for contained research, or field release site perimeters).

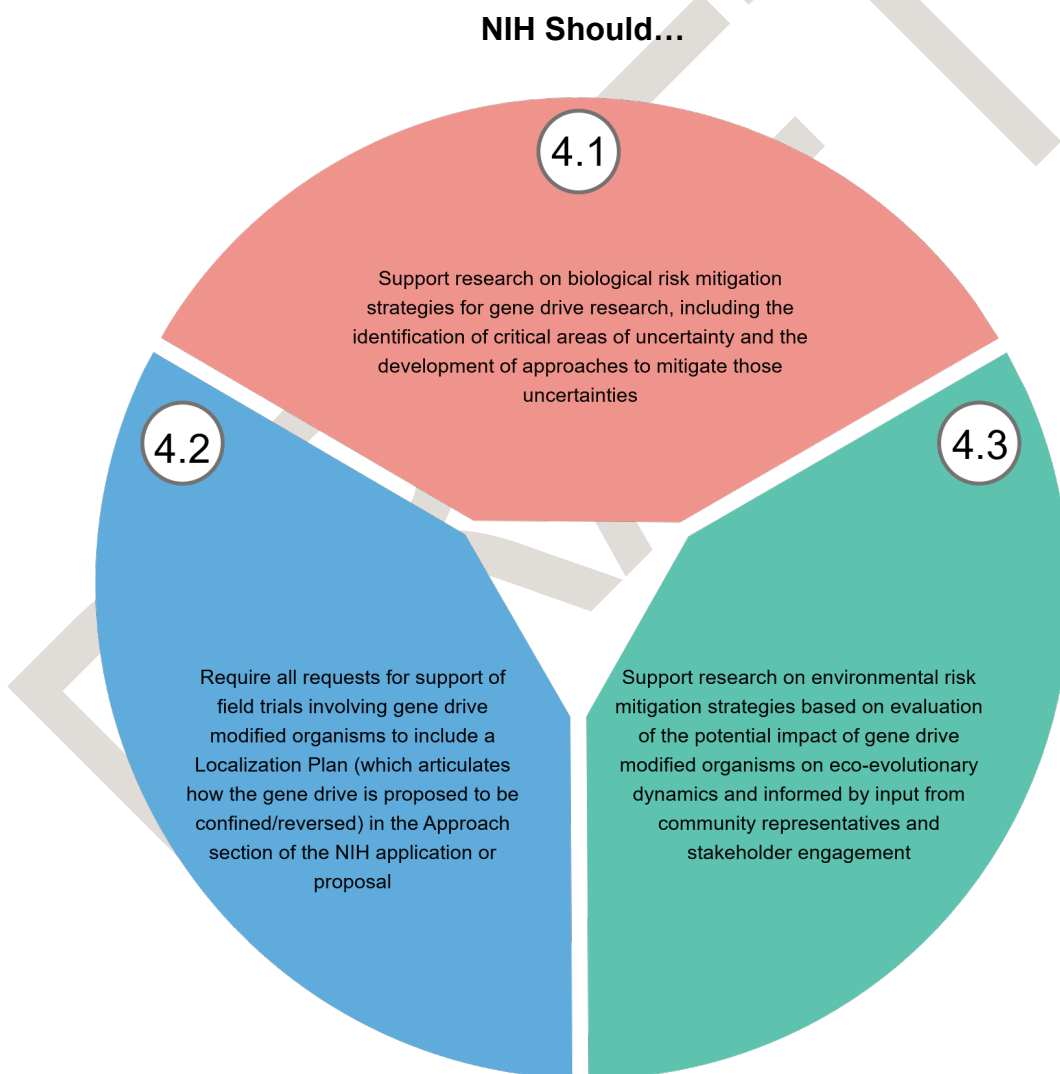
4.3 NIH should support research on environmental risk mitigation strategies based on evaluation of the potential impact of gene drive modified organisms on eco-evolutionary dynamics and informed by input from community representatives and stakeholder engagement.

Prior to the release of gene drive modified organisms at a specific geographical location, an understanding of likely ecological and evolutionary interactions is necessary to inform appropriate risk mitigation strategies. To reduce gaps in such knowledge, support should be provided to a broad range of relevant areas, including population genetics, evolutionary biology, and ecosystems dynamics, as they relate to the potential field release of gene drive modified organisms. Coordination across these disciplines will be required to characterize the genetics of a target population (e.g., subspecies, levels of genetic diversity, genetic connectivity), basic biology of target systems (e.g., breeding cycles, seasonality), ecological data on interacting species, and the environment. Also, the perspectives of local communities and indigenous knowledge is critical to understanding the environmental risk profile for specific locations and communities.

Thus, stakeholder engagement should be part of the development and selection of appropriate risk mitigation strategies for field release applications.

Proven and appropriate risk mitigation strategies are critical for advancing gene drive research responsibly. For research conducted in the laboratory, the inclusion of biological and/or environmental risk mitigation methods in the study design provides additional layers of safety in the event of a breach of physical containment. For NIH to consider support of field release studies that have the potential for broad or lasting impact on the environment, these methods are even more critical.

Figure 3. Recommendations for Biological and Environmental Risk Mitigation Approaches



V. Strategies for Risk/Benefit Assessments for Field Release of Gene Drive Modified Organisms

A. Background

The 2016 NASEM report highlighted the unprecedented potential and challenge of gene drive technologies. While there is enormous potential to reduce transmission of human diseases like malaria, dengue, or Zika by altering the mosquito genome, there are also significant concerns related to the uncertainty of potentially complex ecological impacts.²⁴ Responsible development of these technologies will require comprehensive understanding of how to assess and weigh the potential benefits/harms.

Section III of this report addresses the risk assessment needs for contained research, in considering the adequacy of existing biosafety guidance. While some of the ways to manage risks of field release may rely on some of the same underlying risk mitigation strategies used for contained research, the risk/benefit assessment for planned field releases ranging from contained field trials with large enclosures to broader environmental release poses even greater challenges, especially regarding environmental risks and impacts on communities and the public.

Progression of the field of gene drive research, if it is pursued, will ultimately require that studies move from basic research in contained settings to the release of gene drive modified organisms in field trials.²⁵ The decision by NIH to consider supporting field release research, as well as the review of such studies by regulatory and local authorities that will ultimately determine whether such organisms are approved for release, must rely on rigorous methods for conducting risk/benefit assessments. As with many emerging technologies, gene drive technologies and applications are at a stage of development where there are many uncertainties, including with respect to potential benefits/harms; impacts on the environment, society and economy; and the effectiveness of risk mitigation strategies in preventing or reversing unintended consequences, as discussed in Section IV. Because gene drive technologies are incredibly diverse and complex, robust risk/benefit assessments will need to incorporate and reflect this complexity (e.g., account for the type of gene drive and the existing evidence base related to it, the ecological or environmental setting, considerations specific to the local community).²⁶ The

²⁴ Collins, F. (2016, June 7). *Statement on the National Academy of Sciences Report on Gene Drives in Non-Human Organisms*. U.S. Department of Health and Human Services, National Institutes of Health. <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-national-academy-sciences-report-gene-drives-non-human-organisms>

²⁵ James, S. L., Marshall, J. M., Christophides, G. K., Okumu, F. O., & Nolan, T. (2020). Toward the Definition of Efficacy and Safety Criteria for Advancing Gene Drive-Modified Mosquitoes to Field Testing. *Vector-Borne and Zoonotic Diseases*, 20(4), 237–251. <https://doi.org/10.1089/vbz.2019.2606>

²⁶ Millstone, E. (2009). Science, risk and governance: Radical rhetorics and the realities of reform in food safety governance. *Research Policy*, 38(4), 624–636. <https://doi.org/10.1016/j.respol.2009.01.012>

scope and methods of the risk/benefit assessments will depend on the stage of research along the pipeline from basic research through potential field release (e.g., the level of understanding of the fundamental science underpinning the research, community interests, values and priorities, potential mitigation strategies, and the regulatory landscape).

Confidence in risk/benefit assessment strategies will be essential for NIH to consider when deciding whether to support research involving field release of gene drive modified organisms. The potentially broader and longer-lasting impacts of such research compared to other research with genetically modified organisms or vectors presents new challenges over and above those associated with risk/benefit assessment for other biomedical research. While gene drive research will involve many similar considerations, gene drive research is unique in ultimately spanning a spectrum of potential spread and persistence, which in turn raises issues regarding impact on humans, other populations of organisms, and the environment that are not seen with research involving circumscribable research participant cohorts, or even with other genetically modified organisms not designed to survive outside of containment.

Any risk/benefit assessment for field release of gene drive modified organisms must adhere to the requirements and standards of relevant national and international regulations and norms. In the U.S., the Coordinated Framework for Regulation of Biotechnology²⁷ would apply to research with gene drive modified organisms. Last updated in 2017, the Coordinated Framework describes the roles and responsibilities of the primary agencies involved in regulation of biotechnology products: the FDA (Food and Drug Administration), the EPA (Environmental Protection Agency), and the USDA. Consideration of relevant international guidance and international treaties/organizations (e.g., United Nations (UN) Convention on Biological Diversity,²⁸ WHO Guidance Framework for Testing Genetically Modified Mosquitoes,²⁹ International Union for the Conservation of Nature,³⁰ Cartagena Protocol on Biosafety to the Convention of Biological Diversity³¹) is also important. The ultimate decision regarding permission to proceed with a field release of gene drive modified organisms will lie with local jurisdictions and national regulatory authorities. At a minimum, any field release research study must adhere to relevant regulations. NIH, however, may wish to consider including, as terms of award, additional requirements regarding risk/benefit assessments should field release studies be supported. This point is underscored given that the 2016 NASEM report noted the need for clarity regarding the assignment of existing regulatory authorities.

²⁷ (2017). *Modernizing the Regulatory System for Biotechnology Products: Final Version of the 2017 Update to the Coordinated Framework for the Regulation of Biotechnology*.

https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/2017_coordinated_framework_update.pdf

²⁸ Convention on Biological Diversity. (2019, March 1). *Portal on Synthetic Biology*. <https://bch.cbd.int/synbio>

²⁹ World Health Organization. (2021). *WHO Guidance Framework for Testing Genetically Modified Mosquitoes: Second Edition*. <http://apps.who.int/iris/bitstream/handle/10665/341370/9789240025233-eng.pdf?sequence=1&isAllowed=y>

³⁰ International Union for Conservation of Nature. (n.d.) *Synthetic Biology and Biodiversity Conservation*. <https://www.iucn.org/theme/science-and-economics/our-work/other-work/synthetic-biology-and-biodiversity-conservation>

³¹ Convention on Biological Diversity. (2019, August 8). *Welcome to the Portal on Risk Assessment and Risk Management*. https://bch.cbd.int/onlineconferences/forum_ra.shtml

i. Challenges for Risk/Benefit Assessment

The broad range of potential impacts of release of gene drive modified organisms presents challenges for determining the scope and methods of the risk/benefit assessment. When conducting a risk/benefit assessment, consideration should be given to the following:

- **Balancing potential benefits/harms:** Assessments should focus as rigorously on prospective benefits as on possible harms. For the types of biomedical research supported by NIH, identification of potential public health impacts, especially benefits such as decreasing transmission of vector-borne diseases, will be a critical part of the assessment.
- **Comparing with existing interventions:** Potential public health benefits will need to be considered in the context of existing measures to prevent or treat disease (e.g., mosquito nets for malaria, use of insecticides, potential vaccines).
- **Dealing with ecological and evolutionary complexity:** Ecological risk/benefit assessments, in the context of evolutionary complexity, will be necessary to consider the impacts not only on targeted organisms but also on other populations of organisms (including environmental and ecosystem properties) caused by the potential intended or unintended spread and persistence of gene drive modified organisms. As recommended in the 2016 NASEM report, ecological assessments should adhere to a strategy suited to addressing complex interactions (e.g., large spatial-temporal scales, including seasonality and potential for organism dispersal; competition between species; ecosystem interactions).
- **Considering potential social and ethical benefits/harms:** Risk/benefit assessments should also include potential social, ethical, and economic benefits/harms. For example, it will be important to weigh ethical considerations, including the need for just distribution of potential impacts, to ensure that specific stakeholders do not unfairly bear the burden of harm.
- **Modeling with limited data:** Determining appropriate methods for conducting risk/benefit assessments is also challenging due to the lack of data to address the complexity of gene drive spread in the environment. In situations of high complexity with minimal data, combinations of strategies for qualitative, probabilistic, and/or quantitative assessment may be necessary.³² Even though models are important for assessing strategies, models are only as good as the details and data incorporated (e.g., level of genetic, demographic and ecological complexity, spatial and temporal contexts). Defining uncertainties and setting parameters may be difficult, but possible outcomes and key issues for the assessment will need to be identified. Modeling alone is insufficient; risk/benefit assessments must involve ongoing validation of models with data, as they are accrued, as well as subsequent updating of the models.

³² Kaplan, S., & Garrick, B. J. (1981). On The Quantitative Definition of Risk. *Risk Analysis*, 1(1), 11–27. <https://doi.org/10.1111/j.1539-6924.1981.tb01350.x>

- **Detecting rare events:** Detecting rare events over potentially large spatial and temporal scales will be challenging when monitoring field releases that are limited in size and duration. Conclusions from field tests must be drawn cautiously and subsequent field releases must be monitored.
- **Identifying endpoints with stakeholder and community input:** The input of local and affected communities and stakeholders should be included in the risk/benefit assessment process both for ethical reasons and because such inputs will enhance the assessments.³³ Since currently the development of risk/benefit assessments are often limited to the input of developers, funders, scientific experts, and regulators, broader engagement should be supported so that assessments incorporate input from local and affected communities.
- **Dealing with social and cultural complexity:** Because desired endpoints are always based on values, considering a diverse set of values and interests will be critical to the early stages of risk/benefit assessment. Additionally, knowledge differences and traditions may impact the kind of evidence required to investigate potential benefits/harms.
- **Managing uncertainty:** The management of uncertainty within various risk/benefit assessment models will also reflect values. Strategies for risk/benefit assessment conducted for research in other disciplines involving novel technologies or applications may provide useful models for research involving gene drive. For example, human clinical trial phases may provide a framework and assist in the design of phased field releases and evaluation of gene drive safety (the primary study goal in phase I of human clinical trials research) and efficacy (phases II and III of human clinical trials research). The studies involving the introduction of other genetically modified organisms (e.g., diamond back moth, Oxitec mosquitoes) and *Wolbachia* studies in mosquitoes may also be informative in selecting appropriate models.

In sum, good decision making that is informed by risk/benefit assessments requires familiarity with how those assessments were produced and their limitations.

ii. **Summary of Risk/Benefit Assessment Strategies**

The rapid advances in gene drive technologies that may ultimately result in field release studies require equally rapid progress in the development of risk/benefit assessment strategies. Development of risk/benefit assessments of gene drive modified organisms may draw on experiences with previous assessments for other genetically modified organisms. Gene drive technologies will present similar hurdles in determining the scope of assessments and parameters for models; gathering data to support or modify models; and ensuring input not only from scientists and regulators but also the impacted stakeholders.

³³ Raman, S., Hobson-West P., Lam, M., and Millar, K. (2018). In B. Nerlich, S. Hartley, S Raman, & A. Smith (Eds.), *Science and the Politics of Openness: Here Be Monsters* (pp. 230-250). Manchester University Press. https://www.uib.no/sites/w3.uib.no/files/raman_et_al_2018_science_matters_here_be_monsters.pdf

Unlike other genetically modified organisms, however, the traits of gene drive modified organisms spread and persist in the environment because the genotype is preferentially inherited, and therefore are intended to modify natural populations and may have associated impacts on the environment and society. As such, gene drive modified organisms may require risk/benefit assessments before release that incorporate a broader scope of issues because of the greater uncertainty in terms of potential for both benefits and harms.

B. Recommendations (Figure 4)

In considering the funding of research involving the field release of gene drive modified organisms, NIH should require that phased field trials include a plan for robust risk/benefit assessments at every stage, with the understanding that additional research may be necessary to inform this assessment.

NIH should require all requests for support of field trials involving gene drive modified organisms to:

- 5.1 Include a risk/benefit assessment plan in the Approach section of the NIH application or proposal. Such plans should address the assessment of potential benefits and potential harms, and to whom they would accrue, and identify which environments and which aspects of the environments would be affected.**

The identification of not only potential harms, but also potential benefits, is important to provide a balanced assessment of the impacts of releasing gene drive modified organisms. Benefit assessment should include outcomes that are valued by the impacted communities. Public health assessments should consider not only the potential benefit of the gene drive strategy, but also its relative effectiveness (e.g., whether it has the potential to provide any improvement over existing interventions to manage public health). Ecological assessments should consider the complexity of population genetics, evolution, and ecosystem dynamics. In addition to environmental, ecological, evolutionary, and public health impacts, risk/benefit assessment should also focus on social (e.g., negative public perceptions, potential for backlash leading to mistrust of government or public health authorities) and economic (e.g., tourism or lower availability of products and services for mosquito control) impacts and the ethical implications of manipulating species and ecosystems.

As data will always be lacking, assessments need to consider the availability of scientific and safety evidence and what data are necessary to conduct an adequate assessment. As noted in Section IV, many technologies for biological and environmental risk mitigation are in early phases of development, and at present, it may be difficult to evaluate their effectiveness. Any research that NIH supports to develop effective

risk/benefit assessment strategies must address the availability and adequacy of existing data, and articulate which aspects are based on modeling and predictions.

Additionally, risk/benefit assessments must meet the standards and requirements of the relevant regulatory agencies involved in authorizing an actual field release, and engagement with such agencies should occur early in the process of developing a potential field release study. If a field release is to be funded by NIH, such assessments should incorporate community and public participation in ways that would impact the scope, endpoints, methods, and ultimately, the interpretation of the risk/benefit assessment.

Both qualitative and quantitative methods can be appropriate for risk/benefit assessments for gene drive studies. In situations of great uncertainty, models are necessary to estimate the probability of different outcomes; empirical data will, however, need to be incorporated from laboratory or observational studies to update parameters and probabilities. Any statistical/probabilistic assessments should consider both potential risks and benefits, but simulations alone will not provide adequate risk/benefit assessment.

5.2 Articulate phased research plans with research activities designed to proceed from lower to higher risk in the Approach section of the NIH application or proposal.

The 2016 NASEM report recommended a phased testing pathway for gene drive research. While laboratory research has advanced since the release of this report in 2016, this strategy remains essential to further progress in the area of gene drive research as it approaches the point when field releases might be proposed. As research progresses from laboratory to field release, the data accrued from each phase should feed into the risk/benefit assessment. In an iterative manner through the phases, potential benefits/harms should be identified for designated sites (e.g., laboratory, cages, smaller field, environmental releases), appropriate risk mitigation strategies established, and the data collected used to reassess potential benefits/harms and refine future research. In these phased plans, researchers should also articulate what the impact of the research will be if field release ultimately does not occur (i.e., because of a regulatory decision, local authority decision, outcomes of the risk/benefit assessment, outcomes of community/stakeholder engagement, or other reason), so that there is a plan in place to gain value from the research even if field release does not occur.

5.3 Define milestones for decisions regarding whether to proceed to the next phase, as part of the Approach section of the NIH application or proposal.

Though regulators and local authorities will ultimately decide whether there is permission to conduct field release of gene modified organisms in certain communities, NIH will still determine whether or not to fund (or continue to fund) a study that involves a proposed field release of gene drive modified organisms. The findings from risk/benefit assessments should inform the decision to move to the next phase. Findings should also inform any needed changes to the phased research plan and risk/benefit assessment plan that was submitted with the research proposal, as data become available from earlier phases of the research. Ultimately, of course, benefits should outweigh harms, but the decision to move to the next phase will vary with the context of particular research projects, locations, and communities. Decisions about trials involving the release of gene drive modified organisms should not be driven by a purely quantitative risk/benefit assessment, and appropriate engagement with and input from local communities and affected stakeholders must be included in the assessment.

5.4 Utilize an independent board to provide input on the assessments of potential benefits/harms, milestones, and any associated recommendations for potential field release studies.

NIH should require that, as part of any project involving a field release, risk/benefit assessments be reviewed by a group of individuals with multiple areas of expertise who are independent from the researchers conducting the project. NIH should also consider the appropriate level of independence of the board from NIH itself, to manage conflicts of interests or the appearance of conflicts of interest. Both who is on the board and who convenes it are important aspects to be considered regarding the board's independence. This group should advise on the transition from early to later phases of the research. The group should consider the balance of potential benefits versus potential harms or whether additional evidence is needed to help inform whether the research should proceed to the next phase. Issues of justice regarding how potential benefits/harms may impact different stakeholders and distribution of risk should be included in the group's discussions.

If the research proceeds to field release, the board should continue to monitor the released gene drive modified organism for effectiveness and safety, including the occurrence of adverse or negative impacts to stakeholders or the environment, subject to existing regulations. If negative impacts are detected, the board could advise on mitigation or mechanisms to stop the research. NIH should consider existing mechanisms (such as Data Safety Monitoring Boards) as possible models. While NIH may need to consider different models or mechanisms for this type of board, it would be important that the board has sufficient expertise, local representation (especially for foreign trial sites), and mechanisms for handling conflicts of interest, to be able to advise on the risk/benefit assessment and achievement of milestones during phased testing. Additionally, NIH will need to confer with relevant regulatory and legal authorities

regarding what mechanisms may exist to establish such a board and ensure consistency with existing regulations.

5.5 Make risk/benefit assessments publicly available, as well as any associated recommendations from the independent board, in a timely manner and to the greatest extent allowable by law.

The risk/benefit assessments developed as part of a field release research plan, including associated areas of uncertainty, should be made publicly available. Within legal obligations, NIH should establish terms and conditions of funding that limit non-disclosure of business information and optimize sharing of data and methods.

Transparency in decision making is vital to promoting public trust and engagement. NIH should consider the sources of uncertainty in risk/benefit assessments identified through this process and use that information to inform future research, as appropriate.

NIH's stewardship of novel and exceptional research involves helping to ensure that such research is conducted safely and responsibly. Rigorous and appropriate risk/benefit assessments will be crucial as NIH considers supporting the aim of field release in the context of gene drive research. As articulated in the NIH Director's Statement on the 2016 NASEM Report,³⁴ "NIH clearly has a role in supporting the research to help assess the benefits and risks of gene drives in their application to prevent disease and improve human health."

³⁴ Collins, F. (2016, June 7). *Statement on the National Academy of Sciences Report on Gene Drives in Non-Human Organisms*. U.S. Department of Health and Human Services, National Institutes of Health. <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-national-academy-sciences-report-gene-drives-non-human-organisms>

Figure 4. Recommendations for Risk/Benefit Assessments for Field Release of Gene Drive Modified Organisms

NIH should require all requests for support of field trials involving gene drives to...



VI. Strategies for Stakeholder Engagement Regarding Gene Drive Modified Organisms

A. Background

When plans for research and technology development do not take into consideration the interests, values, goals, and perspectives of the relevant stakeholders, the goals of the research plan are unlikely to be achieved and public trust in science may be diminished. Moreover, gene drive research raises novel ethical considerations related to the types of stakeholders and means of engagement needed, and these considerations differ from those raised by much of the biomedical research typically supported by NIH. These considerations will need to be addressed through iterative stakeholder identification and engagement as part of any NIH decision to support field release research.

In addition to conducting a robust risk/benefit assessment before releasing gene drive modified organisms into the environment, it is critical that researchers proposing field release of gene drive modified organisms engage all relevant stakeholders (including affected communities) regarding the project's goals, potential benefits/harms of the research, and opportunities for shared decision making. As described below, this report takes a broad view of what constitutes a stakeholder in this context, but it also notes the importance of giving appropriate weight to the inputs of individuals or groups that may be most directly affected. It is essential for researchers to assess and understand the interests and values of affected stakeholders in the context of gene drive research in a comprehensive manner, including before proceeding with a field release. Effective engagement leads to an understanding of how the research may impact a wide range of stakeholder interests, both positively and negatively. The goal of engagement is not to persuade stakeholders that the research should proceed; rather, the goals are to 1) identify the relevant interest groups, 2) promote two-way dialogue with stakeholders that includes all viewpoints, and 3) make good-faith efforts to integrate those views into decision-making processes.

i. Role of Stakeholders in Articulating Values, Goals, Potential Benefits/Harms, and Desired Endpoints

While stakeholder input or engagement is often considered to be separate from scientific research and risk/benefit assessment, it is crucial to incorporate it at all phases of the research and development process for new technologies. As such, input from stakeholders should be incorporated into each phase of development of gene drive technologies, from the start of the design phase of a particular gene drive technology, through the risk/benefit assessment and the selection of a field trial site, to the development of a plan for a proposed field release. Different types of stakeholders may have differing views of potential benefits/harms, and different communities may weigh the importance of impacts on the environment or ecology, the economy, or public health differently. As such, addressing concerns raised by communities and

stakeholders may require unique approaches that are tailored to the context of any given project.

ii. Identification of Stakeholders

Research with gene drive modified organisms presents challenges for defining the stakeholder groups to engage. The release of living organisms, which have the potential to spread, may impact a wide range of stakeholders, including some who may be geographically distant from the release site, so researchers should avoid overly narrow definitions of stakeholders that include only geographically proximate communities. It may be difficult to identify all potentially relevant stakeholders, but researchers must make an effort to be as inclusive as possible. Nonetheless, while it is important to be maximally inclusive in engagement, giving a voice to all potential stakeholders, it is also critical to consider how to balance the input from particular groups based on who may be most directly affected (either positively or negatively). It is also important to recognize that those populations that may benefit may be different from those that may be harmed. The prioritization of input from various stakeholders, with the appropriate weight given to their interests and preferences, may be highly dependent on the context of the specific trial.

It may be helpful to identify stakeholders based on related interests, concerns, or level of impact.^{35,36} For example, individuals in the immediate vicinity of a field release will likely have different concerns than the research scientists, whose interests may also be different than those of conservation groups, the media, public health advocates, national or international policy makers, or regulators. Relatedly, engagement strategies should consider identifying stakeholders with a diversity of expertise, especially those with knowledge not represented on the project team. For example, even if Indigenous peoples do not currently occupy the region near a field release site, engagement might include Indigenous representatives who have expertise in traditional ecological knowledge that could be highly relevant to considerations for the release of a gene drive modified organism.

When developing a stakeholder engagement strategy for a possible field release of gene drive modified organisms, it will be important to involve stakeholders who have decision-making roles in local communities, such as mosquito control boards and other regulators.³⁷ Engaging with

³⁵ Thizy, D., Emerson, C., Gibbs, J., Hartley, S., Kapiriri, L., Lavery, J., Lunshof, J., Ramsey, J., Shapiro, J., Singh, J. A., Toe, L. P., Coche, I., & Robinson, B. (2019). Guidance on stakeholder engagement practices to inform the development of area-wide vector control methods. *PLOS Neglected Tropical Diseases*, 13(4), e0007286. <https://doi.org/10.1371/journal.pntd.0007286>

³⁶ Roberts, P., Herkert, J., & Kuzma, J. (2020). Responsible innovation in biotechnology: Stakeholder attitudes and implications for research policy. *Elementa: Science of the Anthropocene*, 8. <https://doi.org/10.1525/elementa.446>

³⁷ Long, K. C., Alphey, L., Annas, G. J., Bloss, C. S., Campbell, K. J., Champer, J., Chen, C.-H., Choudhary, A., Church, G. M., Collins, J. P., Cooper, K. L., Delborne, J. A., Edwards, O. R., Emerson, C. I., Esvelt, K., Evans, S. W., Friedman, R. M., Gantz, V. M., Gould, F., Akbari, O. S. (2020). Core commitments for field trials of gene drive organisms. *Science*, 370(6523), 1417–1419. <https://doi.org/10.1126/science.abd1908>

these key stakeholders early may not only help ensure that the regulatory process proceeds efficiently but also help to identify ways to engage with the broader community.

Finally, an important consideration is determining who has the responsibility to identify and engage relevant stakeholders. Individuals within the research team could play a role in identifying and engaging stakeholders, for example, or a group separate from the researchers could manage this effort. There are benefits and downsides to both options: if those who identify the stakeholders and conduct the engagement are part of the research team, it may be easier to ensure such feedback is well integrated into the research plan; on the other hand, such an approach could also create the potential for bias. These and other factors should be considered when establishing the stakeholder engagement strategy.

iii. Challenges of Stakeholder Engagement

Given the broad range and diversity of potential stakeholders, there may be challenges to conducting effective engagement about a particular study. In clinical trials, the individual research participant makes the decision to participate, and it is the individual who typically bears any risks and consequences of that decision. However, the consequences of gene drive research may be borne by whole communities, animal or plant populations, and ecosystems. Distinct from most research involving human participants (e.g., clinical trials), in which informed consent must be sought from individuals who will be directly involved in providing samples or filling out surveys, or whose property will be involved,³⁸ it is not feasible to seek individual informed consent in the traditional manner from all stakeholders in gene drive research. “Free, prior and informed consent” has been articulated as a process “that attends to issues of transparency, iterative community-scale consent, and shared power through co-development among Indigenous peoples, local communities, researchers and technology developers.”^{39,40} The goal for stakeholder engagement is to obtain collective agreement on whether or not the research should proceed.

Effective stakeholder engagement involves respectful, good-faith communication with all interest groups. A challenge is balancing the various voices that may vie for dominance in the conversation. Individuals who feel strongly, or groups that are highly organized or have sophisticated strategies to amplify their voices, may overwhelm the voices of other stakeholders. Moreover, misinformation can spread easily through social media, damaging the

³⁸ Kolopack, P. A., & Lavery, J. V. (2017). Informed consent in field trials of gene-drive mosquitoes. *Gates Open Research*, 1, 14. <https://doi.org/10.12688/gatesopenres.12771.1>

³⁹ Convention on Biological Diversity. (2017). *Report of the Ad Hoc Technical Expert Group on Synthetic Biology* (p. 17). <https://www.cbd.int/doc/c/7272/69d4/228f63ec4b923f59111580bc/synbio-ahteg-2017-01-03-en.docx>

⁴⁰ George, D. R., Kuiken, T., & Delborne, J. A. (2019). Articulating ‘free, prior and informed consent’ (FPIC) for engineered gene drives. *Proceedings of the Royal Society B: Biological Sciences*, 286(1917), 20191484. <https://doi.org/10.1098/rspb.2019.1484>

accuracy of communications, and leading to misunderstanding about the purpose of the research.⁴¹

iv. Considerations in Stakeholder Engagement

There are numerous examples of stakeholder engagement strategies that have been employed in similar research contexts, such as the release of non-gene drive genetically modified organisms to control invasive species or the use of transgenic agricultural crops.⁴² Recent examples include projects intended to reduce mosquito populations by releasing mosquitoes infected with *Wolbachia*,^{43,44} a bacterium that reduces disease transmission by *Aedes aegypti* mosquitoes, or genetically modified male mosquitoes that produce sterile female offspring.^{45 46} These cases provide important insights into such considerations as the timing of engagement, communication methods, and incorporation of community input into decision-making processes.

In most cases, for engagement to be effective, clear and simple language needs to be developed. It may be important for stakeholders to understand the ultimate goals of the research, even if a specific phase of a trial may have no direct potential benefit or potential harms. In addition to providing scientific details about the potential harms of a specific phase of a field release trial, such as potential harms to native species and broader ecological effects, a key focus of engagement could also be, for example, to convey how a mosquito release may ultimately be of benefit to human health by reducing the incidence of malaria. Overall, however, what, how, and with whom to communicate and engage is likely to be specific to the research context and each proposed field release of gene drive modified organisms.

Appropriate and locally tailored avenues of communication should be used and may include surveys, town halls, in-person events, votes, or other methods. Websites, emails, newsletters, and other virtual communication might be used to keep interested groups informed on a regular basis, but all stakeholders in a given community may not have access to such technology. Importantly, communication must be bi-directional with clear and facilitated processes for stakeholders to ask questions and communicate their interests and priorities. To be effective, the methods and language used must be tailored to different cultures and populations; for

⁴¹ Scheufele, D. A., & Krause, N. M. (2019). Science audiences, misinformation, and fake news. *Proceedings of the National Academy of Sciences*, 116(16), 7662–7669. <https://doi.org/10.1073/pnas.1805871115>

⁴² National Research Council. (2015). Public Engagement on Genetically Modified Organisms: When Science and Citizens Connect: A Workshop Summary. *National Academies Press*. <https://doi.org/10.17226/21750>

⁴³ Centers for Disease Control and Prevention. (2020, September 17). *Mosquitoes with Wolbachia for reducing numbers of Aedes aegypti mosquitoes*. U.S. Department of Health and Human Services. www.cdc.gov/mosquitoes/mosquito-control/community/sit/wolbachia.html

⁴⁴ Callaway, E. (2020). The mosquito strategy that could eliminate dengue. *Nature*. <https://doi.org/10.1038/d41586-020-02492-1>

⁴⁵ Environmental Protection Agency. (2020, June 9). *Issuance of an Experimental Use Permit: Oxitec, Ltd to test efficacy of OX5034 Aedes aegypti mosquitoes expressing tetracycline Trans-Activator Variant (tTAV-OX5034) protein for control of wild Aedes aegypti mosquitoes*. www.govinfo.gov/content/pkg/FR-2020-06-09/html/2020-12372.htm

⁴⁶ Waltz, E. (2021). First genetically modified mosquitoes released in the United States. *Nature*, 593(7858), 175–176. <https://doi.org/10.1038/d41586-021-01186-6>

example, some Indigenous groups may object to being referred to as “stakeholders,” and instead prefer the term, “rights-holders.”^{47,48} As this example illustrates, it is necessary for engagement methods and communication to be informed by the culture and practices of the communities being engaged.

The timing of stakeholder engagement is another important consideration. It is not recommended to wait to engage stakeholders until immediately before an intended field release, as that would prevent input from being considered by investigators, study funders, or regulators. On the other hand, engaging early with methods and communications that are not aligned with the stage of technological development could create confusion and opportunity for misunderstanding or even misinformation. The input of regulators, local leaders, and community groups is essential to achieving optimal experimental design; identifying, articulating and defining desired end points; and contributing to the risk/benefit assessment, so the timing of stakeholder engagement is a critical challenge that should be addressed in planning any proposed field release study.

Ensuring equitable input is fundamental to an effective stakeholder engagement strategy. Various approaches to balance input from competing voices can be employed to address these difficulties when needed, such as the use of a skilled and culturally appropriate facilitator to moderate discussion to ensure that no one viewpoint dominates the conversation. An analytical deliberative process, such as that described in the 2016 NASEM report, can lead to informed discussions, promote a fair process, and build trust. A 2008 National Research Council report on public participation concluded that “when done well, public participation improves the quality and legitimacy of decisions and builds the capacity of all involved to engage in the policy process.”⁴⁹

v. Evaluating Stakeholder Engagement

Stakeholder engagement should be iterative and will need to be conducted before field release data can be accrued to determine the effectiveness of a gene drive. One of the most difficult questions is how to evaluate the extent to which stakeholder engagement has been successful. As discussed above, the goal of stakeholder engagement should not be to persuade stakeholders to “approve” a field release or to get every stakeholder to agree, but rather to identify the relevant interest groups, build lines of communication and trusting relationships, and

⁴⁷ Bull, J., Beazley, K., Shea, J., MacQuarrie, C., Hudson, A., Shaw, K., Brunger, F., Kavanagh, C., & Gagne, B. (2019). Shifting practise: Recognizing Indigenous rights holders in research ethics review. *Qualitative Research in Organizations and Management: An International Journal*, 15(1), 21–35. <https://doi.org/10.1108/QROM-04-2019-1748>

⁴⁸ Sarkki, S., Heikkinen, H. I., & Löf, A. (2021). Reindeer Herders as Stakeholders or Rights-Holders? Introducing a Social Equity-Based Conceptualization Relevant for Indigenous and Local Communities. In D. C. Nord (Ed.), *Nordic Perspectives on the Responsible Development of the Arctic: Pathways to Action* (pp. 271–292). Springer International Publishing. https://doi.org/10.1007/978-3-030-52324-4_13

⁴⁹ National Research Council. (2008). *Public Participation in Environmental Assessment and Decision Making*. National Academies Press. <https://doi.org/10.17226/12434>

incorporate the views of relevant groups into the decision-making process. It is, therefore, important to have a plan for evaluating the outcomes of engagement strategies. Evaluation of engagement can focus on whether value has been generated for stakeholders, harms avoided, and obligations met, and whether meaningful dialogue can continue with interested groups, keeping in mind that such relationships and dialogues may be appropriately scoped to a defined period of time. Finally, when considering funding any proposal for research involving the release of gene drive modified organisms, it is important to ensure that experts in stakeholder engagement are included in relevant proposal reviews so that stakeholder engagement processes and evaluation plans are appropriately reviewed.

vi. Summary of Strategies for Stakeholder Engagement

Stakeholder engagement throughout the course of a study involving field release of a gene drive modified organism is critically important. However, the goal of engagement is not to persuade stakeholders that the research should proceed; but rather, to 1) identify the relevant interest groups, 2) promote dialogue with stakeholders that includes all viewpoints, and 3) integrate those views into decision-making processes.

B. Recommendations (Figure 5)

If NIH has an interest in ultimately supporting research involving field release of gene drive modified organisms, it should act as a vehicle for promoting stakeholder engagement in such research. Given the importance of early planning for research that involves the potential release of gene drive modified organisms, NIH should consider supporting funding mechanisms for project planning that help to set the foundation for such research. NIH should require that stakeholder and community engagement be conducted for all research that proposes field release of gene drive modified organisms. NIH should support research to help establish best practices for successful public engagement simultaneously with studies on gene drive technology. Such research would ultimately be relevant for both laboratory studies and research involving the release of gene drive modified organisms.

6.1 NIH should support planning projects to identify potential trial sites and associated stakeholders, as well as establish, organize, or conduct preliminary engagement activities that could inform future trials.

Given the importance of planning for potential field release research early, and recognizing that funding for such efforts is limited, if NIH intends to support field release research, NIH should support planning mechanisms to allow for identification of appropriate field release sites and engagement of associated stakeholders early. Such approaches could potentially be modeled after NIH's existing R34 planning grants for some clinical trial research.

6.2 NIH should require all requests for support of field release research involving gene drive modified organisms to include a plan for stakeholder and community engagement in the Approach section of the NIH application or proposal. The plan should articulate who will perform engagement activities, as well as how stakeholder and community input would be incorporated into decisions about experimental design and whether to proceed through the phases of the research plan.

Such plans should include:

- a) Identification of community groups that would be directly affected by a gene drive field release (i.e., exposed to any potential benefits/harms)
- b) Strategies for engagement with relevant stakeholder and community groups
- c) Incorporation and consideration of stakeholder and community input during the research phases and in decision-making about field release

Documentation of stakeholders' values and interests, and an explanation of how the research has or will incorporate these factors should be provided in the plan. Ultimately, evidence of community interest and support will be necessary prior to any field release. Consideration should be given to how to meet the needs of certain stakeholder groups, including people living in geographical areas that may have more scientifically desirable conditions for a gene drive field release trial (e.g., islands). For example, field releases of gene drive modified organisms on islands will require stakeholder engagement that addresses historical injustices that have viewed islands and their residents as dispensable and so can be subjected to the risks associated with experimentation.⁵⁰ Historically, Indigenous groups have been marginalized in similar research efforts; integrating Indigenous knowledge and values during the research phases and in decision-making about field release' will be critical.^{51,52} The plan must articulate how stakeholder input will be used to refine the experimental design and inform the decision whether to proceed to the next phase of research and field release. Such research projects should also include experts in stakeholder engagement.

6.3 NIH should support research focused on establishing best practices for stakeholder engagement relevant for either laboratory or field-based gene drive research.

⁵⁰ Taitingfong. (2019). Islands as Laboratories: Indigenous Knowledge and Gene Drives in the Pacific. *Human Biology*, 91(3), 179. <https://doi.org/10.13110/humanbiology.91.3.01>

⁵¹ Working with marginalized groups demands time and respect — and researchers must give both. (2019). *Nature*, 568(7752), 275–275. <https://doi.org/10.1038/d41586-019-01163-0>

⁵² Garrison, N. A., Hudson, M., Ballantyne, L. L., Garba, I., Martinez, A., Tualii, M., Arbour, L., Caron, N. R., & Rainie, S. C. (2019). Genomic Research Through an Indigenous Lens: Understanding the Expectations. *Annual Review of Genomics and Human Genetics*, 20(1), 495–517. <https://doi.org/10.1146/annurev-genom-083118-015434>

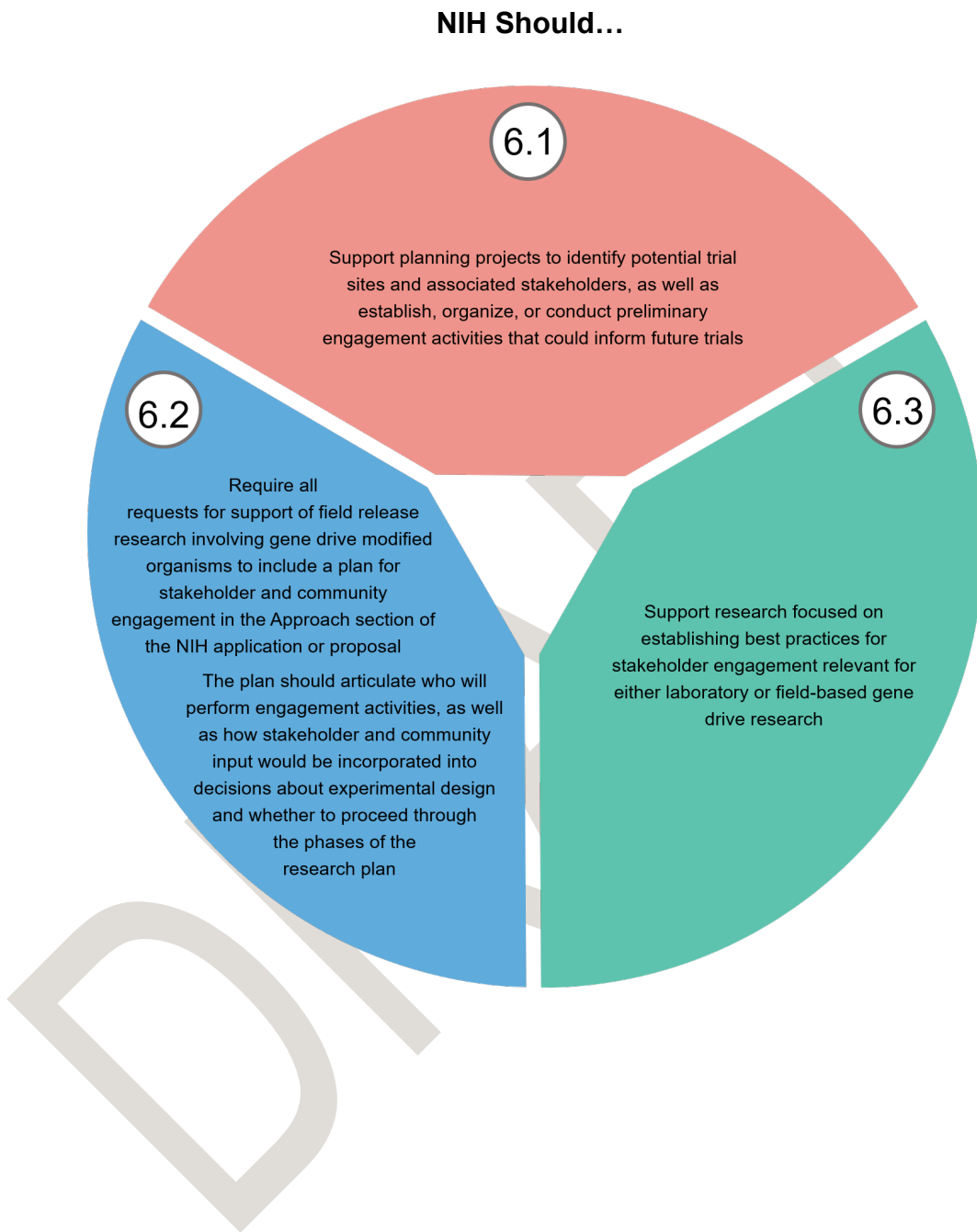
Along with ensuring that stakeholder and community engagement is conducted as part of any NIH-funded research project involving the release of gene drive modified organisms, NIH should support research into strategies for improving stakeholder engagement on gene drive research, in the context of field release research and prior to field release. Such stakeholder engagement research could include:

- a) Identification of key attributes, timing, and post-research evaluation of engagement activities
- b) Identification of novel research partnerships for conducting engagement (e.g., grants with mosquito control boards for deliberation on site selection)
- c) Development of potential frameworks to support iterative engagement strategies.
- d) Examination of ethical and policy issues that are relevant to the conduct of stakeholder engagement in the context of gene drive research

Stakeholder engagement research should include projects that allow for iterative testing so that stakeholder engagement can be evaluated and improved throughout the research project itself and applied to gene drive research in general. NIH could also provide funding mechanisms that allow greater flexibility in setting budgets and modifying research plans in response to what is learned through engagement regarding the interests and values of stakeholders.

NIH support of stakeholder engagement will help to ensure that gene drive field release research, if pursued, is conducted ethically, and it is appropriately informed by relevant stakeholder and community interests and values. It is critical that any field release proposal considers the needs of the local population, the effects it will have on the environment, and the opinions of broader interest groups. Successful engagement will both increase the likelihood of success of field release research, should it be pursued, and strengthen public trust in science and gene drive research.

Figure 5. Recommendations for Strategies for Stakeholder Engagement



VII. Conclusions for Biosafety Guidance for Contained Research and Conditions for Field Release of Gene Drive Modified Organisms

A. Background

The use of gene drive modified organisms, which have the capacity to spread engineered traits through a population rapidly, has not only potential public health benefits but also the risk of potential harms for human health, the environment, and the economy. To help ensure that benefits are maximized, and potential harms are minimized, special consideration is required for both contained research and potential field release research with gene drive modified organisms. While gene drive research continues to advance, there remain gaps in knowledge and implementation related to different types of technologies and applications, risk mitigation strategies, assessment of potential benefits and harms, and stakeholder and community engagement. Such gaps will need to be further addressed as NIH considers funding of research involving field release of gene drive modified organisms. To address these issues, the NExTRAC has focused on examining whether existing biosafety guidance is adequate for contained laboratory research utilizing gene drive technologies and on outlining conditions to be met either before or as part of any potential trial involving field release of gene drive modified organisms.

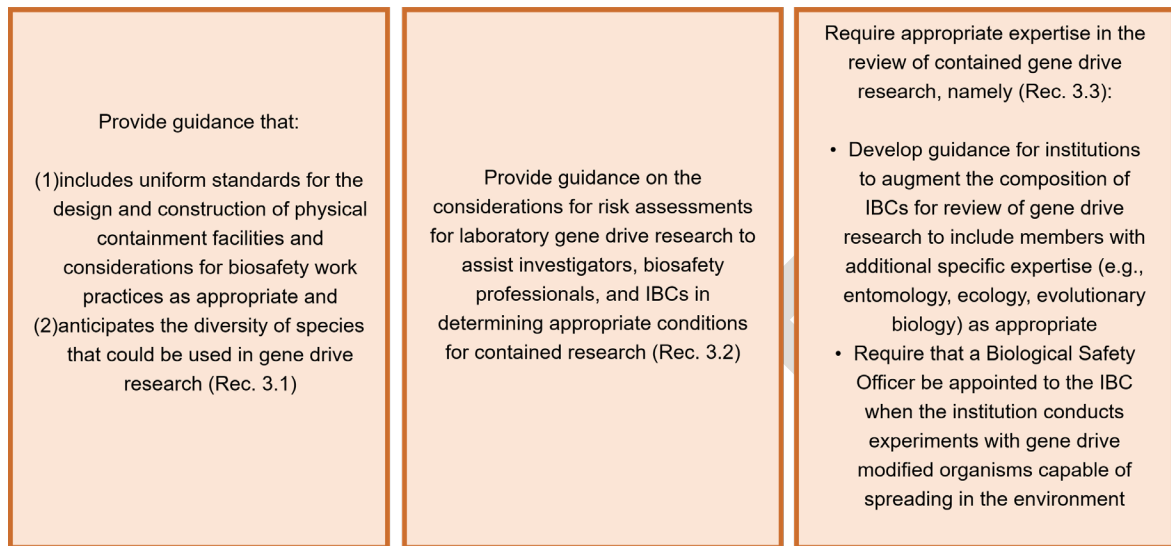
While NIH continues to support laboratory research that uses and advances gene drive technologies, it should develop (or incorporate) biosafety guidance for contained gene drive research, addressing risk assessment, species to be used, and uniform standards for physical containment. To prepare for the possibility that NIH will support research involving the field release of gene drive modified organisms, NIH should support research into key areas of risk mitigation and stakeholder engagement. Ultimately, if NIH decides to support trials involving the release of gene drive modified organisms, NIH should require specific elements to be addressed in research proposals in addition to the experimental design of the trial itself.

B. Overarching Considerations Related to Biosafety Guidance for Contained Research (Figure 6)

The NExTRAC was charged with:

- Considering whether existing biosafety guidance is adequate for contained laboratory research utilizing gene drive technologies.
 - Providing advice on the question: Given the diverse applications and species that may be used in gene drive research with different risks, is the current landscape of biosafety guidance adequate for contained research?

Figure 6. Overarching Considerations Related to Biosafety Guidance for Contained Research



Because U.S. guidance documents do not specifically address biosafety for gene drive research in contained laboratory settings, the Committee recommends that NIH should:

Provide guidance that (1) includes uniform standards for the design and construction of physical containment facilities and considerations for biosafety work practices as appropriate and (2) anticipates the diversity of species that could be used in gene drive research (Recommendation 3.1).

Provide guidance on the considerations for risk assessments for laboratory gene drive research to assist investigators, biosafety professionals, and IBCs in determining appropriate conditions for contained research (Recommendation 3.2).

Require appropriate expertise in the review of contained gene drive research, namely (Recommendation 3.3):

- **Develop guidance for institutions to augment the composition of IBCs for review of gene drive research to include members with additional specific expertise (e.g., entomology, ecology, evolutionary biology) as appropriate.**
- **Require that a Biological Safety Officer be appointed to the IBC when the institution conducts experiments with gene drive modified organisms capable of spreading in the environment.**

C. Overarching Considerations for Field Release (Figure 7)

The NExTRAC Committee was also charged with:

- Outlining conditions (if any) under which NIH could consider supporting field release of gene drive modified organisms.
 - Providing advice on the question: What knowledge and conditions should be in place to ensure that research involving field release of gene drive modified organisms could be conducted safely and ethically?

NIH should consider supporting applications involving the field release of gene drive modified organisms on a case-by-case basis. NIH should only support research involving the field release of gene drive modified organisms when appropriate strategies for risk mitigation, risk/benefit assessments, and stakeholder engagement have been incorporated into the research plan. NIH should support the ability of researchers to develop these strategies by funding research focused on addressing key gaps in knowledge for gene drive research and by defining requirements for the design of field release research proposals.

The following strategies should be developed in the area of gene drive research as NIH considers supporting research involving the field release of gene drive modified organisms:

Biological risk mitigation strategies that are effective in preventing or managing unintended persistence or spread of gene drive modified organisms beyond an intended field release area.

Environmental risk mitigation strategies that can be tailored to various environments with different eco-evolutionary dynamics, taking into account stakeholder interests, values, and concerns.

Stakeholder engagement strategies that address how stakeholder and community input will be incorporated into decisions about site selection, experimental design and whether to proceed through the phases of the research plan. These strategies should integrate appropriate diverse expertise and knowledge (e.g., social science, science communication, humanities) and identify the degree of independence of the engagement team from the technical team.

NIH should contribute to efforts to develop and implement these strategies in the following ways:

Support research on:

- **Effective biological and environmental risk mitigation strategies to limit gene drive spread and undesirable environmental effects (from Recommendations 4.1 and 4.3)**

- **Effective stakeholder and community engagement strategies for laboratory and field release gene drive research (from Recommendation 6.3)**

Support planning projects to identify potential trial sites and associated stakeholders, as well as establish, organize, or conduct preliminary engagement activities that could inform future trials (from Recommendation 6.1).

Finally, NIH should consider requests to fund research involving the field release of gene drive modified organisms on a case-by-case basis, and require that any research proposal involving field release includes specific components to ensure that decision making is informed by biological and environmental risk mitigation plans, risk/benefit assessments, and stakeholder and community engagement. Specifically, NIH should:

Require any research proposal involving field release include in the Approach section of the NIH application or proposal:

- **A localization plan (Recommendation 4.2)**
- **A plan to assess potential benefits/harms – including but not limited to ecological, public health, social, ethical, and economic effects, as appropriate (Recommendation 5.1)**
- **Phased research plans with proposed activities proceeding from lower to higher risk, and with milestones for deciding whether to proceed to the next phase (Recommendations 5.2 and 5.3)**
- **Description of what the impact of the research would be if the research does not ultimately result in a field release (Recommendation 5.2)**
- **A stakeholder and community engagement plan, including identification of stakeholders, description of who will perform engagement activities, description of engagement methods and activities (including how input will be incorporated during research phases), and evaluation of engagement (Recommendation 6.2)**
- **A board, independent from the researchers conducting the project, to provide input on the risk/benefit assessments, milestones, and other aspects of the project in a transparent manner (Recommendations 5.4 and 5.5)**

Proposals for NIH funding of gene drive research should recognize the intersectionality of the required methods for controlling the release of gene drive modified organisms and the need for iteration. Several methods may overlap, and so the proposal should explain how the different components will impact each other. For example, a robust risk/benefit assessment would depend on the interests, values, and inputs of stakeholders to determine what is considered a potential benefit/harm, while the risk/benefit assessment of any field release would help inform dialogue with stakeholders. Additionally, potential ecological/environmental, public health, or economic impacts will be informed by and evaluated based on stakeholder interests and values

that are reflected through stakeholder engagement and dialogue and monitoring the effects of release.

Figure 7. Overarching Considerations for Field Release

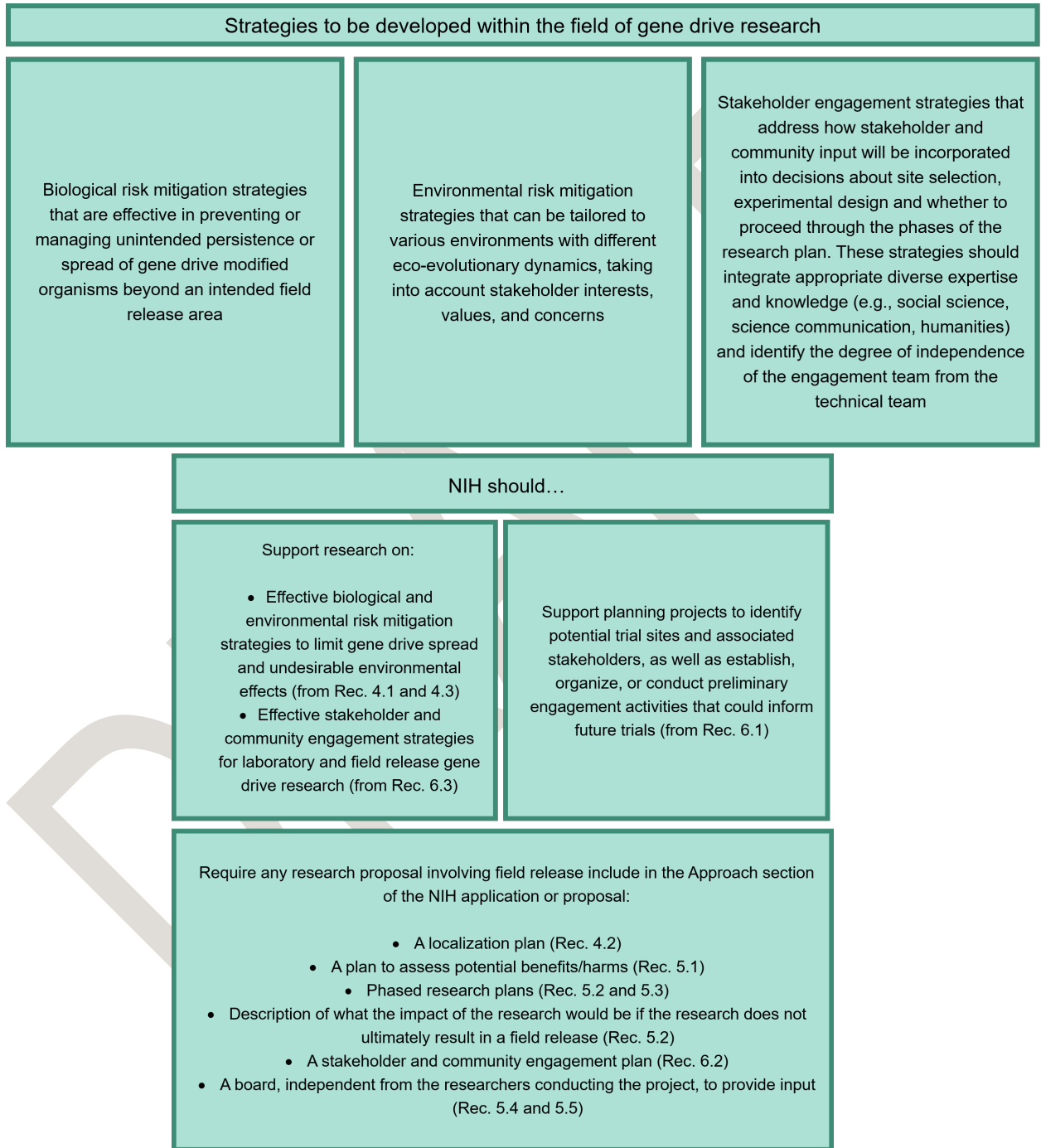
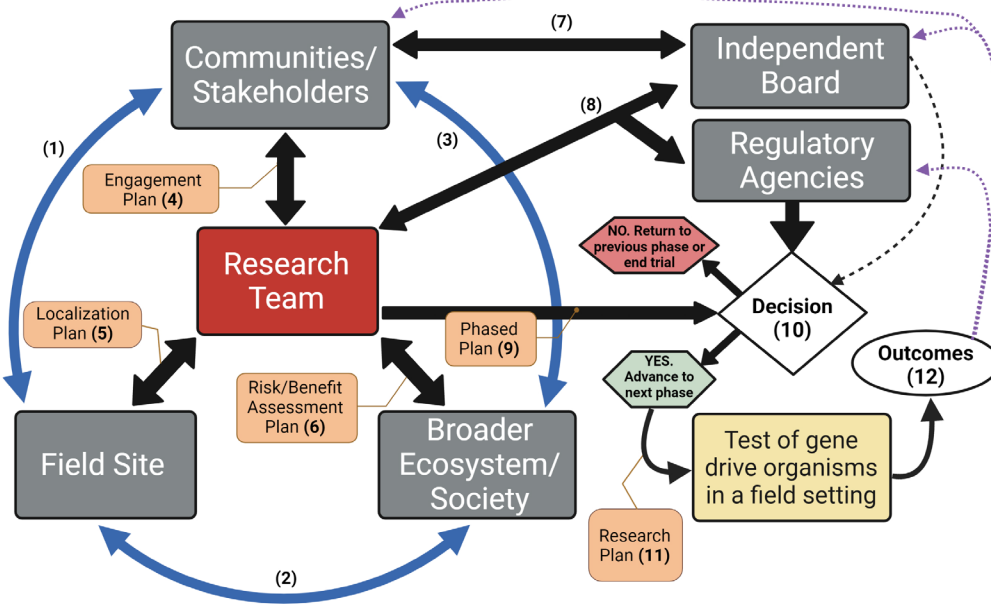


Figure 8. Recommended process and key components of applications to NIH proposing field-based gene drive research



Conceptual representation indicating recommended components of research that involves the field release of gene drive modified organisms. Projects may be designed with multiple phases prior to the initial release of gene drive modified organisms into the environment. Additional phases that build upon any initial releases in scale/scope would be anticipated to follow the same pathway. Arrows indicate connections, influence or feedback between groups or components. Numbering illustrates the various interactions and is not intended to indicate priority, relative importance, or exact order of events.

1. Field site partially defines the organisms, ecosystem properties, and communities/stakeholders that may be directly affected by a proposed trial, while values and concerns of those communities may result in a reevaluation/refinement/relocation of the field site.
2. The field site cannot be separated from the broader ecosystems and aspects of society in which it resides, while these broader considerations in turn influence choice of field site.

3. Community/stakeholder input, interests, and values help define/refine potential risks/benefits and identify protection goals, while potential effects on ecosystems or societies inform who constitutes relevant communities/stakeholders.
4. The research team develops plans to work with communities/stakeholders to gain input into and refine accordingly the proposed research design, while clearly communicating the goals and structure of the project.
5. The research team proposes a field site and develops a plan to restrict gene drive modified organisms/transgenes to that site, refining or altering the proposed site as needed as an evidence-base accumulates.
6. The research team establishes a plan for assessing potential risks/benefits to the environment/public health and refines/alters this plan as evidence is gathered.
7. Communities/stakeholders should be represented on the independent board, while the recommendations of the board, as well any underlying evidence, are made available to communities/stakeholders.
8. The research team provides initial data and plans to relevant regulatory agencies and the independent board, and subsequently revises their plans based on input received. The research team has an obligation to report information to all relevant authorities.
9. The phased plan developed by the research team specifies clear milestones and conditions that must be met in order to proceed with the next phase.
10. When phase milestones appear to have been met, both the relevant regulatory agencies and the independent board decide or advise as to whether the research should proceed to the next phase.
11. If approved by all relevant regulatory and local authorities and incorporating input from the independent board, the research team has the option of proceeding to field release.
12. Outputs of field-testing are communicated with regulatory agencies, the independent board and communities/stakeholders and used to inform consideration of subsequent phases.

D. Summary

Gene drive technologies have a diverse set of potential applications and many potential public health benefits. However, they also come with a range of concerns about possible ecological impacts and potential social and ethical issues.

The NIH has a critical role to play in determining the progress of gene drive research. As a major funder of research that affects public health, the NIH's decision on whether to move research that involves the field release of gene drive modified organisms forward, and the support and guidance it provides to do so, will be an influential factor on this area of research as a whole.

In the contained research setting, gene drive modified organisms may come with unique biosafety considerations. To address these considerations, the development of additional

biosafety guidance regarding physical and biological containment of gene drive modified organisms and the components of effective risk assessment for contained research are important steps to ensuring an adequate landscape of biosafety guidance.

Because gene drive modified organisms are designed to spread in the environment and ultimately to impact both people and environments, there are significant considerations that must be addressed as part of any research project involving field release. Such considerations include the need for additional research on biological and environmental risk mitigation strategies; stakeholder engagement for gene drive research; and support of gene drive research through flexible mechanisms for funding and collaborations. NIH should consider funding research involving the release of gene drive modified organisms on a case-by-case basis, with the recognition that any final decision on whether there is approval to release a gene drive modified organism into the field would ultimately be made by regulators and local authorities. Should NIH choose to pursue funding of research involving the release of gene drive modified organisms, any proposal involving such proposed releases should involve a phased research plan specifying the plans for localization, plans for stakeholder engagement, a risk/benefit assessment, and an independent board to provide guidance as the research progresses. Such proposals should also articulate what the impact of the research will be if field release ultimately does not occur, either due to a regulatory decision, the outcomes of the risk/benefit assessment, or other factors.

APPENDIX 1: Glossary and Acronym Definitions

APHIS	Animal Plant Health Inspection Service	
ACG	<i>Arthropod Containment Guidelines</i>	
ACL	Arthropod Containment Level – There are four ACLs - ACL1 through ACL4.	
Biohazard	A biological hazard, or biohazard, is a biological substance that poses a threat to human, animal, or plant health or to the environment.	
Biological Risk Mitigation	See Containment, Biological.	
Biosafety	The discipline addressing the safe handling and containment of infectious microorganisms, recombinant DNA, and hazardous biological materials.	
Biosafety Level (BL)	In the U.S., four biosafety levels consisting of a combination of laboratory practices, procedures, techniques, safety equipment, and laboratory facilities appropriate for the operations being performed. BL4 provides the most stringent containment conditions, BL1 the least stringent.	
<i>BMBL</i>	<i>Biosafety in Microbiological and Biomedical Laboratories</i>	
BSO	Biological Safety Officer	
Cas9	CRISPR associated protein 9	
Construct	Designed or engineered assembly of DNA sequences.	
Containment	The use of human-made or natural physical restrictions to prevent unintended or uncontrolled release of an organism into the environment.	
	Biological (Also, Biological Risk Mitigation)	The use of highly specific biological barriers or techniques chosen or constructed to limit the transmission, dissemination, propagation, and survival of an organism in the environment. When intended to prevent release, this can be referred to as biological containment; when used as a general strategy (for example, to limit dissemination in a field release), this can be referred to as biological risk mitigation.
	Environmental (Also Environmental Risk Mitigation)	Strategies that use physically or genetically isolated sites to help prevent spread into non-targeted populations. This can be referred to as ecological risk mitigation.
	Physical	The confining of organisms through the use of laboratory practices, containment equipment, and special laboratory design. Emphasis is placed on primary means of physical containment provided by laboratory practices and containment equipment. Special laboratory design provides a secondary means of protection against the accidental release of organisms outside the laboratory or to the

		environment.
Contained Research	Research conducted with gene drive modified organisms that is not intended for release outside a physical laboratory facility that is protected from the outside environment.	
CRISPR	Clustered Regularly-Interspaced Short Palindromic Repeats	
Engagement	Engagement is the "Seeking and facilitating the sharing and exchange of knowledge, perspectives, and preferences between or among groups who often have differences in expertise, power, and values." ⁵³	
	Community	Engagement with a group defined by close geographical proximity to the project site to have tangible and immediate interest in the project.
	Stakeholder	Engagement with individuals that may have personal or professional interests. Stakeholders will vary by location, interest in the project, level of influence, amount they will be affected by benefits and risks, level of expertise, etc.
	Public	Engagement with groups who lack direct connection to a project but have interests, concerns, hopes, fears, and values that can contribute to democratic decision making.
Environmental Risk Mitigation	See Containment, Environmental.	
EPA	Environmental Protection Agency	
Gene Drive	Gene drive refers to technologies whereby a particular heritable element biases inheritance in its favor, resulting in the gene becoming more prevalent in the population over successive generations. Thus, the gene is being "driven" to progressively increase its frequency in the population. Biasing inheritance may involve, for example, more than the familiar Mendelian 50:50 inheritance chance or reducing the fitness of alternative genotypes without directly distorting Mendelian inheritance.	
	High Threshold	Drive designed so that release of large numbers or repeated releases of gene drive modified organism is required for spread of a trait in a population.
	Localized	Drive with limited ability to spread outside of a given area – spatially and/or temporally.
	Low Threshold	Drive designed so that release of low numbers of gene drive modified organisms will result in spread

⁵³ National Academies of Sciences, Engineering, and Medicine. (2016). Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. *National Academies Press*. <https://doi.org/10.17226/23405>

		of a trait throughout a population.
	Modification	Drive designed to introduce or replace a trait in a population.
	Non-Localized	Drive with the ability to spread beyond a given area.
	Self-Limiting	See Localized Drive.
	Split	Gene drive technique in which components (Cas9 nuclease sequence and guide RNAs) are separated on different loci.
	Suppression	Drive designed to spread a trait resulting in reduction or suppression of a population, with some forms resulting in the potential local eradication of a population.
FDA	Food and Drug Administration	
Field Release	Deliberate introduction of a gene drive modified organism into the environment outside of a physical containment.	
IBC	<p>Institutional Biosafety Committee – Under the <i>NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules</i>, the IBC is responsible for the review, approval, and oversight of research with recombinant or synthetic nucleic acid molecules. Responsibilities include conducting an independent assessment of:</p> <ul style="list-style-type: none"> • Containment levels required for the proposed research • Facilities, procedures, and practices • Training and expertise of personnel 	
Informed Consent	<p>Informed consent process involves “three key features: (1) disclosing to potential research subjects information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the research.”⁵⁴ In the context of gene drive research in which not all participants can be communicated with directly, informed consent will involve a process “that attends to issues of transparency, iterative community-scale consent, and shared power through co-development among Indigenous peoples, local communities, researchers and technology developers.”^{55, 56}</p>	
Locally fixed allele (private allele)	An allele that exists only in a specific, usually genetically isolated, population to be modified or a synthetic site introduced into a laboratory population for contained studies.	

⁵⁴ Office for Human Research Protections. (n.d.). *Informed Consent FAQs*. U.S. Department of Health and Human Services. <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/fag/informed-consent/index.html#:~:text=In%20general%2C%20informed%20consent%20of,and%2045%20CFR%2046.117%20respectivel>

⁵⁵ Convention on Biological Diversity. (2017). *Report of the Ad Hoc Technical Expert Group on Synthetic Biology* (p. 17). <https://www.cbd.int/doc/c/7272/69d4/228f63ec4b923f59111580bc/synbio-ahteg-2017-01-03-en.docx>

⁵⁶ George, D. R., Kuiken, T., & Delborne, J. A. (2019). Articulating ‘free, prior and informed consent’ (FPIC) for engineered gene drives. *Proceedings of the Royal Society B: Biological Sciences*, 286(1917), 20191484. <https://doi.org/10.1098/rspb.2019.1484>

MEDEA	Maternal-effect dominant embryonic arrest	
NASEM	National Academies of Sciences, Engineering, and Medicine	
NEXTRAC	Novel and Exceptional Technology and Research Advisory Committee	
NIH	National Institutes of Health	
<i>NIH Guidelines</i>	<i>The NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules</i> specifies biosafety practices and containment principles for constructing and handling recombinant or synthetic nucleic acid molecules.	
NRC	National Research Council	
PPQ	Plant Protection and Quarantine. USDA APHIS program that safeguards U.S. agriculture and natural resources against the entry, establishment, and spread of economically and environmentally significant pests, and facilitates the safe trade of agricultural products.	
Risk	The probability that negative consequences or harm will occur due to exposure to or release of a biological agent.	
Risk Assessment	Process for assessing the potential harms posed by the biological agent and the risks of associated laboratory activities in a contained research setting.	
Risk/Benefit Assessment	Process for estimating the probability of total negative and positive effects based on the evaluation of available data.	
	Ecological	Process for evaluating probability of effects on species, including humans, population, habitat, or ecosystems.
	Environmental	Process for evaluating impacts to environmental aspects.
	Public health	Process for evaluating effects on health of people and communities.
	Socio-economic	Process for evaluating effects on social and economic factors.
Risk Group	<i>NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules</i> classification of biological agents known to infect humans as well as selected animal agents that may pose theoretical risks if inoculated into humans. Included are lists of representative genera and species known to be pathogenic; mutated, recombined, and non-pathogenic species and strains are not considered. Non-infectious life cycle stages of parasites are excluded.	
UN	United Nations	
USDA	United States Department of Agriculture	
WHO	World Health Organization	

APPENDIX 2: Current Biosafety Guidance for Contained Research

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

Since 1976, the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)* have been the framework for biosafety oversight for research with recombinant and synthetic nucleic acid molecules. The *NIH Guidelines* apply to research that is conducted at or sponsored by any institution that receives NIH funding for projects involving recombinant or synthetic nucleic acid molecules. Several other Federal agencies require compliance with the *NIH Guidelines* as a term and condition of their funding. Some institutions also voluntarily adhere to the requirements of the *NIH Guidelines*.

The purpose of the *NIH Guidelines* is to specify safety practices for constructing and handling recombinant or synthetic nucleic acid molecules. The *NIH Guidelines* specifically address research conducted in contained settings and are not applicable to non-contained research such as field releases of transgenic organisms.

Institutions subject to the *NIH Guidelines* must establish an Institutional Biosafety Committee (IBC) for the review of recombinant and synthetic nucleic acid research. IBCs at many institutions are also assigned responsibilities beyond those articulated in the *NIH Guidelines* and by their institutions and may often review other research with biohazard risks.

Biosafety in Microbiological and Biomedical Laboratories (6th Edition)

The Centers for Disease Control and Prevention (CDC) and NIH jointly publish the biosafety guidance document *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*. The purpose of the *BMBL* is to recommend best practices for the safe conduct of work in biomedical and clinical laboratories from a biosafety perspective. Like the *NIH Guidelines*, the *BMBL* primarily addresses contained laboratory research. The focus is heavily on human pathogens, but there is a chapter on agricultural pathogen biosafety and the *Arthropod Containment Guidelines* are also incorporated by reference. The *BMBL* includes a discussion of biological risk assessment which describes approaches to assessing risks and selecting appropriate safeguards.

Arthropod Containment Guidelines (Version 3.2)

The *Arthropod Containment Guidelines (ACG)* were developed by members of the American Committee on Medical Entomology, a subcommittee of the American Society of Tropical Medicine and Hygiene. The document is a reference for research laboratories to assess risk and establish protocols for the safe handling of arthropod vectors of human and animal disease agents. Risk assessment principles are outlined to establish an appropriate

arthropod containment level (ACL 1-4). For each ACL, guidance is provided for standard practices, special practices, safety equipment and facilities.

Containment Guidelines for Nonindigenous Phytophagous Arthropods and Their Parasitoids and Predators (2002)

The USDA APHIS *Plant Protection and Quarantine (PPQ) Containment Guidelines* are a reference to help entities design, build, maintain, and operate facilities for containing nonindigenous, phytophagous arthropods and their parasitoids and predators. The standards articulated in the document are used by USDA APHIS PPQ personnel when inspecting and issuing a permit for a facility to determine whether the facility meets appropriate containment standards.

World Health Organization Laboratory Biosafety Manual (4th Edition)

The *World Health Organization (WHO) Laboratory Biosafety Manual* provides guidance on laboratory biosafety techniques including good microbiological practices and procedures and use of biosafety equipment. The document addresses risk assessment, control and review, core requirements for biosafety, options for heightened control measures, maximum containment measures for very high-risk operations, transfer and transportation of infectious substances, biosafety program management, laboratory biosecurity, and national and international biosafety oversight. The fourth edition adopts a risk- and evidence-based approach to biosafety rather than a prescriptive approach to ensure that laboratory facilities, safety equipment and work practices are locally relevant, proportionate and sustainable. Emphasis is placed on the importance of a “safety culture” that incorporates risk assessment, good microbiological practice and procedure and standard operating procedures, appropriate introductory, refresher and mentoring training of personnel, and prompt reporting of incidents and accidents followed by appropriate investigation and corrective actions.

Table 3 - Comparison of Current Key Biosafety Guidance Documents

	<i>NIH Guidelines</i> (April 2019)	<i>Athropod Containment Guidelines</i> (Version 3.2)	<i>BMBL</i> (6th Edition)	<i>PPQ Containment Guidelines for Nonindigenous Phytophagous Arthropods and Their Parasitoids and Predators</i> (2002)	<i>WHO Laboratory Biosafety Manual</i> (4th Edition)
Scope	Biosafety practices and containment principles for constructing and handling recombinant or synthetic nucleic acid molecules	Reference for assessing risk and establishing protocols for the safe handling of arthropod vectors of human and animal disease agents	Best practices for the safe conduct of work in biomedical and clinical laboratories	Reference for designing, building, maintaining, and operating facilities to prevent the release of nonindigenous, phytophagous arthropods and their parasitoids and predators	Guidance manual to assist countries to implement basic concepts in biological safety and develop national codes of practice for the safe handling of pathogenic microorganisms in laboratories
Applicability	Research conducted at or sponsored by any institution receiving NIH funding for recombinant or synthetic nucleic acid molecule research from the NIH. Some other federal agencies may also require compliance with the <i>NIH Guidelines</i> as a term and condition of their funding	Voluntary code of practice	Voluntary code of practice	Condition of USDA APHIS PPQ permit approval	Voluntary code of practice
Regulation/ Requirement/ Guidance	Condition for NIH funding of recombinant or synthetic nucleic acid molecules	Guidance/ standard of practice	Guidance/ standard of practice	Regulatory requirement. Release is a violation of the Plant Protection act and is subject to civil and/or criminal penalties and loss of permits	Guidance/standard of practice

Specifically Addresses Gene Drive Modified Organisms	Yes, if generated using recombinant or synthetic nucleic acid molecules	No	No	No	Briefly addresses genetically modified organisms (Section 8)
Defined Biosafety Levels	Yes, describes BSL1- BSL4 (Appendix G)	Yes – Arthropod Containment Levels (ACL) 1-4	Yes, describes BL1- BL4 (Section IV)	No	No, but describes core requirements, heightened control measures and maximum containment (Sections 3,4,5)
Containment Facility Requirements / Standards	Yes, describes facility and equipment requirements. (Appendix G)	Yes, describes facility and equipment requirements	Yes, describes facility and equipment requirements. (Section III and Appendix A)	Yes, describes detailed construction standards (Sections II and III) and equipment standards (Section IV)	Yes, describes facility design and laboratory equipment (Sections 3, 4, 5)
Risk Assessment Guidance	Yes (Section II)	Yes, discusses principles of arthropod risk assessment	Yes (Section II)	No, only address physical containment standards	Yes (Section 2)
Detailed Guidance on Practices and Procedures	Yes. Standard practices and special practices (Appendix G)	Yes, standard and special practices	Yes, describes standard and special and procedures (Section III)	Yes, describes operational standards (Section V)	Yes, Good microbiological practice and procedure, etc. (Sections 3, 4, 5)
Oversight Requirements	Institutional Biosafety Committee review, approval, and ongoing oversight required for covered research	No	No	USDA APHIS inspections and approval	No, but recommends a Biosafety Committee review work and to ensure biosafety policies are followed consistently (Section 7)
Biological Safety Officer	Required to be appointed to IBC when conducting specific types of research (Section IV-B-3)	No	Recommended (Section 2)	No	No, but recommends a Biological Safety Officer provide advice and guidance to personnel and management on biological safety issues. (Section 7)