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### Core commitments for field trials of gene drive organisms

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## POLICY FORUM

## BIOTECHNOLOGY GOVERNANCE

# Core commitments for field trials of gene drive organisms

We must ensure that trials are scientifically, politically, and socially robust, publicly accountable, and widely transparent

By **Kanya C. Long, Luke Alphey, George J. Annas, Cinnamon S. Bloss, Karl J. Campbell, Jackson Champer, Chun-Hong Chen, Amit Choudhary, George M. Church, James P. Collins, Kimberly L. Cooper, Jason A. Delborne, Owain R. Edwards, Claudia I. Emerson, Kevin Esvelt, Sam Weiss Evans, Robert M. Friedman, Valentino M. Gantz, Fred Gould, Sarah Hartley, Elizabeth Heitman, Janet Hemingway, Hirotaka Kanuka, Jennifer Kuzma, James V. Lavery, Yoosook Lee, Marce Lorenzen, Jeantine E. Lunshof, John M. Marshall, Philipp W. Messer, Craig Montell, Kenneth A. Oye, Megan J. Palmer, Philippos Aris Papatianos, Prasad N. Paradkar, Antoinette J. Piaggio, Jason L. Rasgon, Gordana Rašić, Larisa Rudenko, J. Royden Saah, Maxwell J. Scott, Jolene T. Sutton, Adam E. Vorsino, Omar S. Akbari**

Gene drive organisms (GDOs), whose genomes have been genetically engineered to spread a desired allele through a population, have the potential to transform the way societies address a wide range of daunting public health and environmental challenges. The development, testing, and release of GDOs, however, are complex and often controversial. A key challenge is to clarify the appropriate roles of developers and others actively engaged in work with GDOs in decision-making processes, and, in particular, how to establish partnerships with relevant authorities and other stakeholders. Several members of the gene drive community previously proposed safe-

guards for laboratory experiments with GDOs (1) that, in the absence of national or international guidelines, were considered essential for responsible laboratory work to proceed. Now, with GDO development advancing in laboratories (2–5), we envision similar safeguards for the potential next step: ecologically and/or genetically confined field trials to further assess the performance of GDOs. A GDO's propensity to spread necessitates well-developed criteria for field trials to assess its potential impacts (6). We, as a multidisciplinary group of GDO developers, ecologists, conservation biologists, and experts in social science, ethics, and policy, outline commitments below that we deem critical for responsible conduct of a field trial and to ensure that these technologies, if they are introduced, serve the public interest.

A broad array of GDOs are in development, including those that are geographically localized, nonlocalized, temporally self-limiting, and self-propagating (see the first table). CRISPR/Cas9-based editing has expanded not only the types of GDOs that are possible (2–5) but also the societal challenges they may help to solve. In particular, major threats to human health may be eliminated by reducing the viability of and/or inducing resistance to pathogens in mosquitoes such as *Aedes* spp. (major vectors of dengue, chikungunya, and Zika viruses) and *Anopheles* spp. (major vectors of malaria parasites), or in white-footed mice (carriers of the Lyme disease bacterium). GDOs for suppression of pest populations could also contribute greatly to biodiversity conservation, agricultural productivity, and human and animal well-being.

The core commitments presented here (see the second table) are intended to address field trials of either localized GDOs (i.e., GDOs that are genetically or molecularly confined so that they will not spread indefinitely) or nonlocalized GDOs in ecologically isolated locations (e.g., limited-access islands located beyond GDO dispersal capacity, or targeting of a private allele that exists only in an isolated population). Although determinations of whether a GDO is sufficiently confined and who should make these decisions will need to be considered for each GDO and field trial site, introductions of nonlocalized GDOs into sites that are not ecologically isolated would be beyond the scope of these guidelines. We also recognize that these commitments are not enforceable in a regulatory sense; even so, we pledge to apply these commitments to our own practices, recognizing the inherent complexity of this work and our intent to contribute to a fair and ethical culture of gene drive research. These commitments are congruent with guiding principles ad-

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## Characteristics and examples of gene drive organisms

Two broad types of engineered approaches exist to modify populations; one requires gene drive and the other relies on non-drive technologies. Multiple examples of these types of systems exist, which can have varied temporal dynamics, including Self-Propagating (with a low threshold; predicted to spread from a GDO release that represents a small percentage of the target population), Majority Wins (with a high threshold; predicted to spread into a population only when the transgene is present in >50% of the target population), and Self-Limiting (temporally limited; can only spread or persist in a population for a short period). These systems can fall under two broad categories: Nonlocalized (predicted, on the basis of a lack of genetic/molecular confinement, to spread beyond boundaries) and Localized (predicted, on the basis of genetic/molecular confinement, to spread only within a localized population).

APPROACH	EXAMPLES	TEMPORAL DYNAMICS	GEOGRAPHIC REACH
Gene drives	Linked-homing#, Medea, CleaveR, TARE/TADE#	Self-Propagating (low threshold)	Nonlocalized
	Translocations, Tethered Homing, Underdominance#, UD <sup>MEL</sup> *	Majority Wins* (high threshold)	Localized
Non-drives	Daisy#, split-homing#, killer rescue, Homer	Self-Limiting (temporally limited)	
	SIT#, RIDL#, fsRIDL#, pgSIT#		

#Can be used for population suppression in some forms. \*Although UD<sup>MEL</sup> does have a high threshold, it does not always fall under Majority Wins temporal dynamics. Abbreviations: Medea, maternal effect dominant embryonic arrest; TARE/TADE, toxin-antidote recessive embryo/toxin-antidote dominant embryo; CleaveR, Cleave and Rescue; UD<sup>MEL</sup>, maternal effect lethal underdominance; SIT, sterile insect technique; RIDL, release of insects carrying a dominant lethal; fsRIDL, female-specific release of insects carrying a dominant lethal; pgSIT, precision-guided sterile insect technique. See supplementary materials for more details and references.

opted by several organizations with interests in GDO research (6–8). We extend these principles specifically to decisions on whether and how to conduct GDO field trials, which will require new and expanding collaborations. To become a signatory to these guiding principles, please visit [www.geneconveni.org/supporters-of-the-core-commitments-for-field-trials/](http://www.geneconveni.org/supporters-of-the-core-commitments-for-field-trials/).

Although field trials of GDOs ultimately will depend on public policy decisions, those engaged in GDO work can play critical roles in support of these decisions by generating evidence and developing evaluation strategies in fair and effective partnerships with relevant authorities and other stakeholders. That the authors of this paper are based largely in high-income countries reflects the current reality that GDO development is occurring primarily in such countries. However, fair partnership with counterparts and communities in low- and middle-income countries where many GDOs have the highest potential for positive impact underlies each of our commitments, as does recognition of the need for capacity-building and global cooperation.

#### FAIR PARTNERSHIP AND TRANSPARENCY

Fair partnership among GDO developers, communities where GDOs may be released, regulators (government officials charged with making decisions about whether and how GDOs can be tested locally, even when the regulatory pathway for GDOs may not yet be fully defined), and stakeholders and other experts (6) is critical and will require substantial time and resources (9). These stakeholders will be engaged in all stages of trial preparation (10, 11) and are integral to partners' understanding of existing and required scientific and regulatory capacities of each partner community or country and its political and cultural context. In addition, field site characteristics—such as disease incidence or pest exposure, vector or pest species distributions, and target population genetic background, ecology, and connectivity to surrounding populations—will require input from various stakeholders.

This engagement will help to identify the best forms for multidirectional communication and learning, appropriate processes for obtaining government authorization and determining community-level agreement, and meaningful methods to ensure accountability among partners. GDO teams and local and national partners will co-define and collect baseline data needed for each trial, and will prepare an early-response team to address observations in trial-relevant measures. A media commu-

nication plan and platform for rapid dissemination of data and interim analyses to field site partners, nongovernmental organizations, and globally interested parties (e.g., open-access journals) should be considered. Plans to provide information on progress and adjustments in the trial,

**“We pledge to apply these commitments to our own practices ... to contribute to a fair and ethical culture of gene drive research.”**

including changes in the release strategy or discontinuation of the study, will be determined in partnership with trial-site community members and government authorities. Transparency about funding, as well as coordination among members of more than one potential release site, is encouraged. In addition, we will work toward a global public registry for communities and laboratories intending to develop GDO applications. This presents challenges in design, implementation, and enforcement of such a registry, including the need to respect the amount of information disclosed. We commit to both these principles of openness and working to establish the tools and methods needed to facilitate fair partnership and transparency. We believe that this work will support project partnerships broadly but should be considered essential for GDO trials.

#### PRODUCT EFFICACY AND SAFETY

Evidence of laboratory efficacy will be demonstrated prior to a GDO release (12). A draft target product profile (TPP), or similar format, detailing acceptable performance parameters and characteristics of the GDO should be prepared by the developer in consultation with regulators [e.g., (13)]. Evidence of efficacy in the laboratory should include fitness of GDOs, effective release thresholds, stability (i.e., driving capacity maintained over generations), reduction in ability to transmit locally circulating pathogens, and breeding trials with wild strains, as applicable. Results of laboratory cage experiments will help to identify additional data needs.

Guidelines proposed in 2015 addressed important biosecurity considerations for laboratory-based GDO research (e.g., laboratory gene drive experiments should use at least two stringent confinement strategies) (1). With our expectation that these considerations will already have been ad-

ressed before moving toward field testing, we focus here specifically on safety considerations for field testing. Tests of product safety should be conducted prior to, during, and after the release of GDOs, given that natural selection will function during each stage. Recognizing that no action or inaction can be entirely risk-free, required safety levels will be jointly defined with partners, neighboring communities, and regulatory institutions. For example, GDOs' potential to damage or alter closely related or otherwise key species should be examined. Results of experiments assessing both efficacy and safety should be made publicly available within a reasonable time frame. We commit to co-defining safety with trial partners and to openly sharing data on efficacy and safety of a GDO.

#### REGULATORY EVALUATION AND RISK/BENEFIT ASSESSMENT

At a minimum, conducting GDO field trials requires adherence to existing, and often evolving, national (or, in some cases, subnational) regulations and regional and international agreements. Developers will submit required analyses (variously known as risk, safety, and/or environmental assessments) to regulators and respond to their requests, recognizing that regulatory pathways may still be in development. Trial protocols will be reviewed for approval by local ethics boards, institutional review boards, and/or animal care and use committees. Regulators may also require protections of communities where GDOs are released, such as maintaining existing control methods or instituting these methods as a backup to GDOs, and these protections (e.g., use of insecticides or pesticides) should be incorporated into trial design.

We believe risk assessment for GDO field trials should include two methodological innovations. First, new methodologies are needed to assess potential social, epidemiological, and ecological benefits and their distribution. Second, we aspire to broaden risk/benefit assessment and make it more inclusive than traditional assessments that rely on expert-defined health and environmental risks, and to explicitly consider issues that may be harder to measure, such as justice. A Procedurally Robust Risk Assessment Framework (14) is one model for expanding assessments to include risks of relevance to the social, cultural, and political context. We recognize the value of integrating indigenous and other types of local expert knowledge (15), examining socioeconomic risks, and encompassing risks and benefits of introducing or not introducing GDOs in these assessments.

## Core commitments for field trials of gene drive organisms

### Fair partnership and transparency

- Partner with collaborating communities, local experts, and stakeholders to increase quality of field trial design and ensure accountability
- Integrate community and stakeholder perspectives into interim analyses of field trials and possible considerations of trial redesign or termination
- Present timely data on open platforms and work toward a global registry for GDOs

### Product efficacy and safety

- Support the establishment of acceptable performance parameters of a GDO in collaboration with partner communities and regulators
- Identify sources of uncertainty and their potential influence on estimates of safety and efficacy
- Make efficacy and safety data publicly available

### Regulatory evaluation and risk/benefit assessment

- Engage early and often with regulators, following national regulatory procedures and regional and international agreements to obtain ethics and regulatory approvals
- Develop methodologies to enable evaluation of potential benefits and their distribution
- Expand risk/benefit assessments to be more inclusive of multiple types of knowledge and expertise through engagement with local communities and other stakeholders

### Monitoring and mitigation

- Engage and partner with community members, regulators, and experts to prepare monitoring and mitigation plans
- Define conditions under which mitigation strategies should be deployed and prepare local infrastructure for potential mitigation efforts
- Openly report field, modeling, and laboratory data on GDO safety and effectiveness in field conditions

## MONITORING AND MITIGATION

GDO developers should engage and partner with communities, regulators, evolutionary biologists, ecologists, and social scientists to prepare and participate in surveillance for effectiveness and safety, and to monitor unintended consequences before, during, and after release, with accountability to various partners delineated before a field trial. Measures of GDO success will be defined before release and may include evidence of continuing biological function (e.g., prevalence of the transgene in the target population), evidence of elimination of the target population, and evidence of epidemiological, evolutionary, or ecological impacts related to a pathogen or pest. Monitoring systems will be co-designed for early detection of, for example, inadvertent introgression of the transgene into neighboring populations of the target organism or select nontarget species. They will include collection of genetic and/or genomic data of target species prior to release to be compared with post-release populations, so as to understand gene flow and genetic diversity and to characterize potential resistance alleles. Ecological studies are also critical to understanding breeding behavior and other key parameters that may affect field trial protocols.

Early all-season modeling of releases at the trial site will help to inform data collection goals, including the geographic and temporal scope of collections, with a buffer zone around the immediate release site depending on the biological characteristics (e.g., dispersal range) of the target species and ecological isolation of the trial site. The length of time needed to demonstrate efficacy and safety of the GDO for wider use will be established at the beginning of the trial, aided by mathematical models. Considerations will include data needed for possible geographic scale-up. Monitoring during field trials will initially include rates of gene drive persistence and spread and will later inform epidemiological or ecological impacts. For trials with epidemiological endpoints, sufficient clinical capacity should be established early in trial design to assess changes in disease incidence.

Plans for risk management—in the event of undesired escape of a transgene to neighboring communities or nontarget species; development of resistance in vector, pest, or pathogen; or unintended effects that persist in the population—will depend on the drive construct used and on input from communities, ecologists/scientists, and regulators. Before trial initiation, triggers and risk management

strategies will be clearly defined. Capacity for rapid community-wide use of a chosen vector/pest countermeasure should be established, including stocking of chemical control agents (e.g., pesticides) and personnel capacity needed for implementation. The need for social remediation (i.e., responsiveness to social harm/disruption) should be addressed in the risk management plan. Use of countermeasures such as self-limiting systems (see the first table) or drive removal technologies may be considered, with these systems made available and laboratory-tested, with similar framework and rigor, before the trial begins.

By presenting our commitments for field trials of GDOs, we aim to prepare for potential field trials that are scientifically, politically, and socially robust, publicly accountable, and widely transparent. Our intent is to contribute to public policy decisions on whether and how to proceed with GDOs, based on evaluations conducted in fair and effective partnerships with relevant authorities and other stakeholders. We recognize our responsibility to work openly; we acknowledge that many innovations beyond those in the laboratory are still needed; and we welcome others, including a broad array of stakeholders in partner countries, to join us in conversation about appropriate governance of this technology and to advance together equitably, safely, and responsibly.

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## SUPPLEMENTARY MATERIALS

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## Supplementary Materials for

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Disclosure statements

Table 1 with full references

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## Disclosure statements

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**Table 1 with full references**

Approach	Examples	Temporal Dynamics	Geographic Reach
Gene Drives (16, 17)	Linked-homing <sup>#</sup> (2, 4, 18–21), Medea (22–24), CleaveR(25, 26), TARE/TADE <sup>#</sup> (27, 28)	Self-propagating (low threshold)	Non-localized
	Translocations(29, 30), Underdominance <sup>#</sup> (31), UD <sup>MEL</sup> * (32), Tethered Homing (33)	Majority wins* (high threshold)	Localized
	Daisy <sup>#</sup> (34), split-homing <sup>#</sup> (1, 3, 35–37), Homer (38, 39), killer rescue (40, 41)	Self-limiting (temporally limited)	
Non-Drives	SIT <sup>#</sup> (42), RIDL <sup>#</sup> (43), fsRIDL <sup>#</sup> (44), pgSIT <sup>#</sup> (45)		

**Table 1. Characteristics and examples of engineered population control technologies.** Two broad types of engineered approaches exist to modify populations—one requires gene drive and the other relies on non-drive technologies. Multiple examples of these types of systems exist, which can have varied temporal dynamics including: Self-propagating with a low threshold (predicted to spread from a small release), to majority wins with a high threshold (predicted to spread into a population only when the transgene is present at >50%), to self-limiting which are temporally limited (can only spread or persist in population for a short period). These systems can fall under two broad categories from non-localized (predicted to spread beyond boundaries) to localized (predicted to spread within a localized population). For more details on the various examples and terminology see associated references. <sup>#</sup>Can be used for population suppression in some forms. \*While UD<sup>MEL</sup> does have a high threshold it does not always fall under “majority wins” temporal dynamics. Abbreviations: Medea, maternal effect dominant embryonic arrest; TARE/TADE, toxin-antidote recessive embryo/toxin-antidote dominant embryo; CleaveR, Cleve and Rescue; UD<sup>MEL</sup>, maternal effect lethal underdominance; SIT, sterile insect technique; RIDL, release of insects carrying a dominant lethal; fsRIDL, female-specific release of insects carrying a dominant lethal; pgSIT, precision-guided sterile insect technique.

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