Core commitments for field trials of gene drive organisms

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Abstract

This concise statement of core commitments from a multidisciplinary community will, if followed, promote responsible conduct for confined field trials of gene drive organisms.

Introduction

Engineered gene drive organisms (GDOs) have the potential to transform the way societies address a wide range of daunting public health and environmental protection challenges. Development, testing, and implementation of GDOs, however, is complex and often controversial. A key current challenge is clarifying the appropriate roles of developers and others actively engaged in work with GDOs in decision-making processes.

The following statement represents an initial articulation of commitments from a multidisciplinary group of developers and experts in ancillary fields who agree on the need for responsible development and testing of GDOs to ensure these technologies serve the public

interest. Our commitments are based on the understanding that, while field trials of GDOs ultimately will depend on public policy decisions, members of this group 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 who might share these commitments. The authorship of this statement reflects the current reality that GDO development is occurring primarily in high-income countries. However, fair partnership with counterparts and communities in low- and middle-income countries where many GDOs have the highest potential for positive impact, as well as recognition of the need for capacity-building and global cooperation, underlies each of our commitments.

CRISPR editing provides great potential to democratize the development of GDOs, whose genomes have been genetically engineered to spread a desired genetic trait through a population. Many such systems are in development (*1–4*) as tools for eliminating major threats to human health 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), *Anopheles* spp. (major vectors of malaria parasites), or 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. Although a desire for expeditious release of GDOs to address pressing global health and ecological needs is understandable, a GDO's propensity to spread necessitates well-developed criteria for field trials to assess their potential impacts safely (*5*).

In 2015, members of the gene drive community, including several represented here, proposed safeguards for laboratory experiments with GDOs (*6*). In the absence of national or international guidelines, such safeguards were considered essential for responsible laboratory work to proceed. Now, with the establishment of GDOs in laboratories (*1–4*), similar safeguards are envisioned for the next step: ecologically and/or genetically confined field trials to assess the performance of GDOs. While some coauthors would apply additional requirements, collectively, we consider the commitments outlined here to be critical criteria for responsible conduct of a GDO field trial.

Our Commitments

A broad array of GDOs, from geographically localized, to non-localized and temporally self-limiting, to self-propagating, are in development (Table S1). Analogous to laboratory biosafety levels for managing risks associated with pathogen work, increasingly stringent commitments apply to the release of GDOs that require greater caution and these should be reviewed on a case-by-case basis. The core commitments presented here are intended to address field trials of either non-localized GDOs in ecologically isolated locations (e.g., limited-access islands located beyond GDO dispersal capacity; or targeting a private allele), or localized GDOs (i.e., genetically confined). Introducing a non-localized GDO into a non-ecologically isolated site would be considered an 'open release' requiring more stringent standards and likely additional commitments. Our core commitments are congruent with the

guiding principles adopted by several organizations sponsoring or supporting GDO research (*5*, *7*, *8*).

Trial co-development and transparency

Open and sustained communication among GDO developers, communities where GDOs may be released, regulators, and stakeholders and other experts (terms previously defined (*5*))—a process of trial co-development—is critical and will require a significant commitment of time and resources (*9*). These stakeholders will be engaged in all stages of trial preparation (*10*) and are vital for obtaining a comprehensive understanding of existing and required scientific and regulatory capacities of the partner community and country, political and cultural context, field site characteristics such as disease incidence or pest exposure, vectors or invasive species that are co-circulating, population genetic background and ecology of the target populations (e.g., population subdivision and genetic diversity), and degree of geographical isolation of the possible trial site.

Before, during, and after release of a GDO, the developers will work with engagement specialists and other experts to engage community and government partners, as well as other relevant stakeholders, who are interested in adoption of, or have the reasonable potential to be affected by, the GDO (*5*, *11*). This will help determine the best forms for multi-directional communication and learning, appropriate processes for obtaining government authorization, community consent, and methods to ensure accountability among partners. GDO teams with local and national partners will co-define and collect baseline data needed for each trial, and prepare an early response team to address observations in trial-relevant measures (e.g., GDO efficacy). A media communication plan and platform for rapid dissemination of data and analyses to field site partners (e.g., cloud services), and globally interested parties (e.g., open access journals), should be considered. Updates on progress and adjustments in the trial, including changes in the release strategy or discontinuation of the study, will be discussed with trial-site community members. Transparency in terms of funders and 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. Although there remain significant uncertainties about the design, implementation, and enforcement of such a registry, including the need to respect partner communities in information disclosed, we agree on the value of working toward this goal.

<u>Core commitments:</u>

- ➢ Incorporate input from collaborating communities, local experts, and stakeholders to increase quality of field trial design and ensure accountability
- ➢ Integrate community and stakeholder perspectives into regular assessments of field trial results and possible need for trial redesign or termination
- ➢ Present timely data on open platforms and work toward a global registry for GDOs

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 identify additional data needs.

Safety will also be a principal consideration during product development, and tests should be conducted prior to, during, and following the release of GDOs given that natural selection will act on each stage. Recognizing that no action or inaction can be entirely risk-free, what counts as “safe enough” will be jointly defined with partner neighboring communities and regulatory institutions. For example, GDOs' potential to increase disease, 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 timeframe.

Core commitments:

- ➢ 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

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 termed risk, safety, and/or environmental assessments) to regulators and respond to their requests, and 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 in communities where GDOs are released, such as maintaining existing control methods previously used at the trial site or instituting traditional control methods as backup, and these should be incorporated into trial design.

We believe risk assessment for GDO field trials should include two methodological innovations. First, new and innovative methodologies are needed to assess potential social, epidemiological, and ecological benefits, and their distribution, of a GDO application. 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. Assessments should include risks of relevance to the social, cultural and political context, and will require engagement with local communities and other stakeholders (*14*). We recognize the value of integrating indigenous and other types of local expert knowledge (*15*), examining socio-economic risks, and encompassing risks and benefits of not deploying GDOs or introducing alternatives.

Core commitments:

- ➢ Engage early and often with regulators, following national regulatory procedures and regional and international agreements to obtain ethical 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

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 organism), elimination of the target organism, and epidemiological, evolutionary, or ecological impacts related to the 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 non-target species. They will include collection of genetic and/or genomic data of target species prior to release to be compared with post-release populations to understand gene flow and genetic diversity and to characterize potential resistance alleles. Ecological studies are also critical to understand breeding behavior and other key parameters that may affect field trial protocols. Early all-season modeling of releases at the trial site will help 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 GDO 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 non-target species, development of resistance in vector, pest, or pathogen, or unintended effects that persist in the population—will depend on the drive construct employed and discussions with communities, ecologists/scientists and regulators. Prior to 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 technologies (Table S1) or second-generation GDOs designed to either suppress or replace the previous GDO may be considered (Table S1), with these systems made available and laboratory-tested, with similar framework and rigor, prior to the initiation of the trial.

Core commitments:

- ➢ 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 efficacy in field conditions

In conclusion, gene drive research in the laboratory is advancing, and the establishment of fair partnerships among all developers, ancillary experts, stakeholders, and decision-making authorities is needed to ensure responsible, safe, ethical, and accountable field trials. By presenting our commitments for field trials of GDOs, we aim to prepare for scientifically, politically and socially robust, publicly accountable, and widely transparent field trials of GDOs. In composing this document, 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 continued conversation as we advance together safely.

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Signatories*

*We will determine these signatories once the final draft is accepted by journal. Example agencies we hope to include: FNIH, NIH, USDA-NIFA, USDA, EPA, WHO, Gates Foundation, TIGS, Gene Drive Research Outreach Network, UCIMI, Target Malaria, GBIRd, Island Conservation, USFWS.

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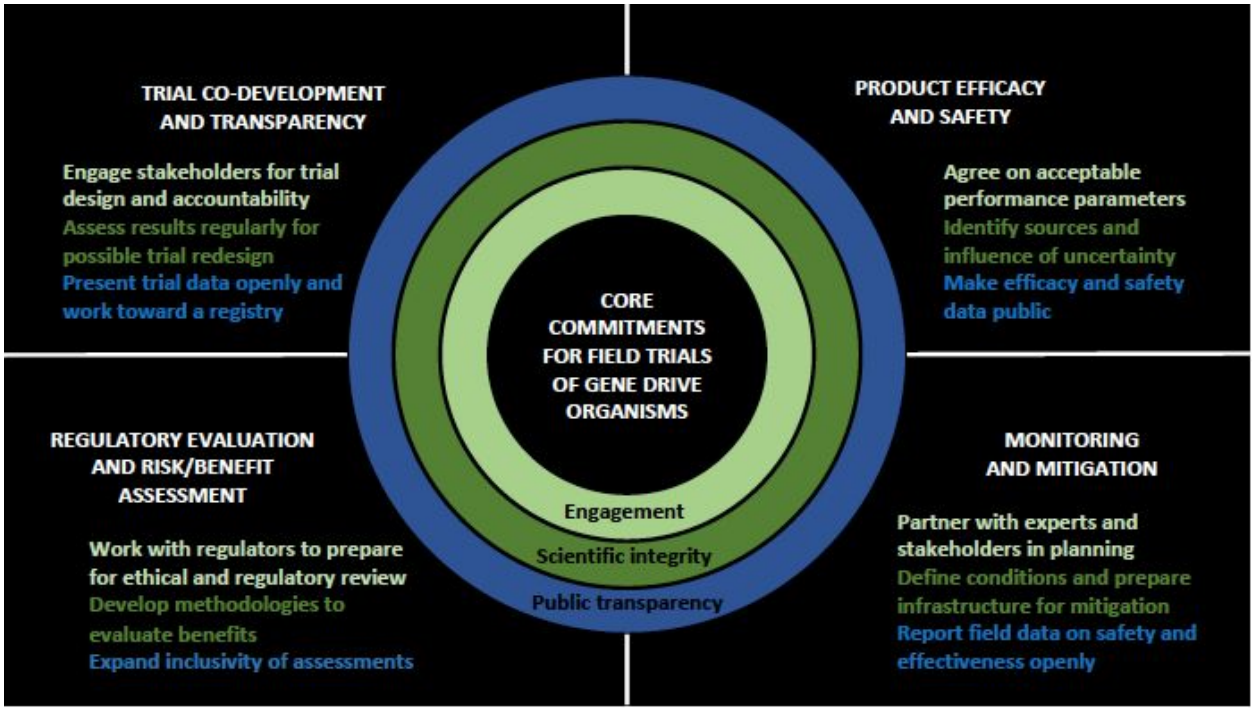
Figure 1. Core Commitments for Field Trials of Gene Drive Organisms



<table>
<tr><th>Approach</th><th>Examples</th><th>Temporal Dynamics</th><th>Geographic Reach</th></tr>
<tr><td rowspan="3">Gene Drives</td><td>Linked-homing#, Medea, CleaveR, TARE/TADE#</td><td>Self-propagating (low threshold)</td><td>Non-localized</td></tr>
<tr><td>Translocations, Underdominance#, UD$^{MEL*,\#}$</td><td>Majority wins* (high threshold)</td><td rowspan="3">Localized</td></tr>
<tr><td>Daisy#, split-homing#, killer rescue</td><td rowspan="2">Self-limiting (temporally limited)</td></tr>
<tr><td>Non-Drives</td><td>SIT#, RIDL#, fsRIDL#, pgSIT#</td></tr>
</table>

Table S1. 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. #Can be used for population suppression in some forms. *While UD^{MEL} does have a high threshold it does not always fall under "majority wins" temporal dynamics.

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