Policy Brief

Monitoring gene drives after release

Engineered gene drive approaches could be a potential solution to address global health and conservation challenges. By selecting a trait to spread rapidly through a species via sexual reproduction over several generations, engineered gene drives could for example, reduce a target mosquito population or its capacity to transmit diseases such as malaria. In conservation, engineered gene drives can support the elimination of invasive alien species (IAS) threatening native ecosystems and carrying infectious diseases (see What's a Gene Drive?).

While no engineered gene drive organisms have been released in the environment yet, discussions about monitoring considerations after release are already taking place. Some of these include monitoring objectives (i.e., entomological, epidemiological, or environmental aspects), ideal features of indicators and parameters, roles and responsibilities, among others.

A monitoring plan is meant to confirm ongoing stability, safety, and effectiveness (for the intended use) of a living modified organism (LMO), such as an engineered gene drive organism, over time and space in the field. It is designed to help developers assess whether any changes in the organism deserve attention and whether adjustments in this technology management are needed. Overall, monitoring efforts for gene drives aim to help collect data to inform decisions and management of organisms post-release.

POLICY RECOMMENDATIONS

- National authorities are responsible for providing guidance and setting the requirements for monitoring gene drives after release. Although no gene drive organisms have been released in the environment yet, governments can build on existing guidelines and previous experiences on how to monitor other genetically modified organisms. National authorities should also work in collaboration with gene drive developers and other stakeholders for the design and implementation of monitoring activities.

- Gene drive technology is designed to propagate specific genetic modifications through a target population, with the potential to spread and persist in the environment. These unique characteristics must be taken into consideration when designing the monitoring plan, as gene drive organisms released in a given country may spread beyond national borders. A regional approach to managing transboundary monitoring needs, which includes data portability and harmonization and supports countries at different levels of preparedness, is recommended.

- Countries interested in using gene drives need to build capacity. Adequate investments should be directed towards developing regulatory frameworks, infrastructure, and human capital necessary for the implementation of monitoring plans. Additionally, investments in capacity-building, information sharing, and technology transfer are crucial to enhance a country's capacity to use gene drive technologies.

How should we monitor gene drives organisms after release?

There are many different types of gene drive constructs, for many different uses and contexts. Monitoring plans should be consistent with the principle of case-by-case evaluation, proportional to the associated risk. These plans must be tailored to a specific organism, the modification that it carries, and the environment in which it is released. They should also consider the types of indicators, parameters, and magnitude of change that should signal concern.

As there have not been releases of gene drive organisms to date, there is currently no prior experience of monitoring gene drive organisms after release. However, existing guidance and experiences can inform monitoring activities. For example, the WHO's Guidance Framework for Testing Genetically Modified Mosquitoes, though focused on genetically modified non-gene drive mosquitoes, outlines principles that are broadly relevant to potential gene drive species for health and conservation purposes.

The Framework includes considerations for monitoring throughout the development and deployment pathway of genetically modified mosquitoes. According to WHO, while most characteristics monitored in gene drive mosquitoes are similar to those of any other genetically modified organisms, some of them are unique. These include molecular properties, phenotypic stability, and fitness. These properties would have to be monitored on a

case-by-case basis, proportional to the associated risk.

National authorities will also need to specify monitoring factors in terms of approval ahead of a release, detailing the required monitoring activities, their duration, frequency, and reporting intervals, including any provision for reporting adverse events.

The WHO emphasizes the importance of engaging regulators, developers, and other stakeholders in defining monitoring requirements for gene drives. As gene drives have the potential to spread across large geographical areas that can span multiple political and ecological boundaries, leveraging existing regional programs – which include, for example, cross-border networks for data-sharing - could help design efficient and scalable monitoring strategies. When creating a monitoring plan, it is also crucial to build on existing groundwork, conducted throughout the technology development pathway, such a data from laboratory studies, field evaluations and risk assessments.

The Cartagena Protocol on Biosafety of the Convention on Biological Diversity (CBD) also serves as a guiding framework for designing monitoring plans, particularly in the context of transboundary movement of LMOs, including gene drives. The Protocol addresses issues of information sharing, legal frameworks including regional and multilateral arrangements and agreements, and capacity- building for the safe transfer, handling, and use of LMOs. The work under the CBD on identification and monitoring of LMOs is also relevant, as building capacity to detect and identify gene drive organisms is relevant to the capacity to monitor post-release (see submission to the CBD).

WHAT CAN WE LEARN FROM THE RELEASE OF NON-GENE DRIVE ORGANISMS?

There is also a substantial body of knowledge related to monitoring of deliberate release of (non-gene drive, non-GMO) organisms used for biocontrol purposes. This information can provide valuable insights for developing monitoring protocols for gene drive LMOs.

> Oxitec, a biotechnology company, uses genetically modified mosquitoes to suppress wild populations of Aedes aegypti. In 2017, the National Institute of Public Health and the Environment (RIVM) in the Netherlands carried out a biosafety evaluation of this technology following guidance for risk assessment of genetically modified animals by the European Food Safety Authority (EFSA). Oxitec's post-release monitoring protocols in the Cayman Islands, Malaysia, Brazil, and Panama provided insights into what should be the purpose, process, frequency and release rates, responsibilities, and tools of monitoring programs. Two main trapping methods were employed: ovitraps (egg catch), as recommended by WHO for Aedes aegypti surveillance, and BG sentinel traps, though less densely. Post-release, vector control organizations monitored mating competitiveness, mosquito dispersal, longevity, and persistence of modified genes to ensure that there were no unintended effects on human, animal health and the environment. On the Island of Saba, In Saba, it was advised that an independent party conduct monthly checks until the modified mosquito population fell below detectable levels, following WHO guidelines.

Target Malaria, a research consortium that aims to develop and implement innovative genetic technologies to reduce the population of malaria-transmitting mosquitoes, has also documented useful information on monitoring, after their small-scale release of non-gene drive, genetically modified, sterile male mosquitoes in the village of Bana, Burkina Faso. While the objective of the release was a preliminary estimation of dispersal distance and field site readiness for future GMM releases, it also provided insights into post-release monitoring protocols, with particular focus on the role of local communities in the monitoring process. Prior to the release, monitoring committees were established to ensure community involvement prior to, during, and after the release. A 20-day "Mark-Release-Recapture" (MRR) comparative study was carried out. Following the MRR, regular monthly monitoring assisted by molecular analyses continued for seven months, to detect the presence of genetically modified mosquitoes at the release sites.

The Australian release of Wolbachia-infected Aedes aegypti mosquitoes, a primary dengue vector, also provides a precedent for monitoring of disease vectors. According to O'Neill SL, Ryan PA, Turley AP et al (2018), up to to 172 BG-Sentinel (BGS) traps were used weekly for sample collection for morphological identification as part of the monitoring process. The mosquitoes collected were tested to determine their Wolbachia infection status. As the project advanced, monitoring shifted to fortnightly collection before concluding with long-term annual assessments.

Monitoring plans to consider national contexts and regulations

Dialogue between developers, regulators, and other stakeholders is key for defining appropriate monitoring requirements. Developers' expertise, for example, is critical for discussions about practical monitoring approaches and relevant parameters. Their insights, combined with information from other stakeholders and voluntary guidelines, help shape effective monitoring strategies. Ultimately, post-release monitoring plans for gene drives will greatly be influenced by issues raised during risk assessments, including stakeholders' inputs, as well as conservation goals and national concerns and priorities.

Key considerations for a post-release monitoring plan of gene drive organisms

A monitoring plan should be feasible at scale within available resources, capable of detecting signals of concern, proportionate to the identified risks, and able to provide evidence of ongoing product effectiveness. This requires the necessary regulatory frameworks, infrastructure, and human and financial resources to implement and oversee the monitoring activities.

A robust, informative, and sustainable monitoring plan could consider the following questions:

Core question	Complementary questions
What to monitor?	• What are the parameters to be monitored? • What information from the risk assessments need to be factored in the monitoring plan? • How will transboundary movement be monitored?
Where to monitor?	• How will releasing area monitoring be done? • Which other areas will be monitored and how?
How to monitor?	• What is the proposed methodology for carrying out the monitoring? • What is available in existing guidance and what is not available? • What jurisdictional guidance is available?
Who will monitor?	• What is the role of regulators and developers? • What is the role of bordering countries? • Who are the other stakeholders? Do they have a role to play?
Can we monitor?	• What capacity is available? Is it adequate? • What capacity needs to be developed? • Are there sufficient financial resources?

CONCLUSION

As gene drive research progresses rapidly, it is important that discussions on post-release monitoring advance accordingly to ensure enough consideration is given to the core questions highlighted above. Collaborative efforts among all stakeholders are imperative to reach a consensus on how to effectively monitor gene drives after their release.

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