TARGET MALARIA

A Vector Control Research Alliance

Target Malaria's response to the NAS Recommendations in:

'Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values'

Target Malaria is seeking to develop an innovative tool for vector control to help put an end to the burden of malaria in Africa. The project is researching the use of gene drive technology to reduce the population of malaria-carrying mosquitoes to levels sufficiently low to interrupt transmission. We recognise that the application of gene drive technology has tremendous potential, but also raises questions that need to be addressed constructively and thoroughly before any gene drive-based product can be considered for use.

Target Malaria welcomes the guidance and considerations offered by the US National Academy of Science in its report "Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values". Several of the recommendations highlighted by the report are already being implemented by Target Malaria. In order to advance responsible gene drive research, the project has undertaken to examine how it meets the recommendations and, where gaps exist, outline how it can improve its practices. We expect to be able to update this response as the project progresses.

5. Phased Testing and Scientific Approaches to Reducing Potential Harms of Gene Drives

5-1: Scientists conducting research on gene drives should follow a phased testing pathway, a step-by-step framework that begins with developing a research plan and continues through, if applicable, monitoring gene-drive modified organisms in the environment. Each phase in such a pathway should include pre-defined "go/no-go" decisions for determining whether to transition to the next phase based on evidence regarding harms and benefits, efficacy, and safety.	Target Malaria has adopted a staged approach for its research and development, gradually moving from genetically modified sterile males *An. gambiae* (that are not gene drive-based) through to a self-sustaining modified *An. gambiae* based on gene drive. In each phase, the mosquitoes go through several steps for testing for both safety and efficacy. Currently, Target Malaria teams are designing a number of gene drive constructs for population suppression of *An. gambiae*, and testing them in the lab in single crosses and small cages for homing rates and fitness (esp. fertility) effects. We are also currently designing additional assays for resistance and off-target effects.

	Our testing pipeline will also include multi-generation fitness assays in larger, more realistic cages, reaction norms across a range of temperatures, and various safety tests (for e.g., effects on insecticide resistance and vector competence). Using mathematical modelling to predict impact on disease transmission, a target product profile is being developed to define the characteristics that our constructs must meet for further development. These assays are still being developed, and we are not yet at the stage of having precise quantitative go/no-go criteria.
5-2: Whenever possible researchers should use available datasets and models to develop and evaluate strategies to minimize the potential for harmful off-target and non-target effects throughout the phased testing pathway.	The elements outlined in 5.2 are already implemented in Target Malaria's planned activities. However, Target Malaria believes it is important to go beyond what is currently available and gather new empirical data relevant to these issues. We are currently in discussion with potential collaborators to develop assays for off-target cleavage events, similar to those that have been developed for human cells. We are also developing a research programme to investigate the ecological relationships of *An. gambiae* with other species, to allow more informed predictions about the potential impact of suppressing or eliminating them from a region.
5-3: Whenever possible, researchers should use a split gene drive in laboratory studies to avoid issues associated with a failure of containment.	This recommendation is primarily directed at those working with model organisms like *Drosophila*. In Target Malaria's case, since we seek to build gene drive constructs for use in nature, we must use intact (non-split) constructs. We recognise this poses specific containment challenges and so, to ensure containment, we have both robust physical containment and are using 'ecological' containment by carrying out the safety testing work in areas where the target species cannot establish.

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5-4: Whenever possible, researchers should include a gene drive that spreads a visible marker to distinguish modified organisms and facilitate research and monitoring.	Target Malaria is currently using a dominant visible marker in all its gene drive constructs, and is currently considering the potential to use a unique marker that distinguishes gene drive constructs from others. Looking ahead, we are considering the best methods to track our mosquitoes following field releases; further data, modelling, and discussions with regulators will inform the development of these methods.
5-5: Researchers, regulators, and other decision-makers should not rely upon a "reversal" gene drive as the sole strategy for mitigating the effects of another gene drive.	Target Malaria considers this recommendation as essential. A comprehensive risk management strategy is needed for all products, which includes thorough risk assessment before release, of which a phased and staged approach will be an important component. This exercise will allow us to define the plausible potential harms, and plan the appropriate mitigation strategies for each one. In the (unlikely) case it would be needed, a driving construct causing population suppression can be incapacitated by the release of very simple resistant or suppressor constructs that would spread rapidly by conventional natural selection (analogous to the spread of insecticide resistance), without any need for drive. These suppressors could be as simple as a non-coding RNA that incapacitates the gene drive construct. We will be assessing such mechanisms before any field release of a gene drive construct.
6. Assessing Risks of Gene-Drive Modified Organisms	
6-1: Researchers, regulators and other decision-makers should use ecological risk assessment to estimate the probability of immediate and long-term environmental and public health effects of gene-drive modified organisms and to inform decisions about gene drive research, policy, and applications.	As outlined in section 5, thorough risk assessments are part of the step-by-step approach of Target Malaria. The project has already worked with an independent body (CSIRO) for a quantitative ecological risk assessment around keeping its male-sterile strain in insectaries in Africa (specifically, risks resulting from accidental escapes), and we will continue this practice for each step of the pipeline up to release of a gene drive construct.

6-2: To strengthen future ecological risk assessment for gene-drive modified organisms, researchers should design experimental field trials to validate or improve cause-effect pathways and further refine ecological models.	Target Malaria is currently developing a research programme to investigate the ecological relationships of *An. gambiae* with other species, to allow more informed predictions about the potential impact of suppressing or eliminating them from a region.
6-3: To facilitate appropriate interpretation of the outcomes of an ecological risk assessment, researchers and risk assessors should collaborate early and often to design studies that will provide the information needed to evaluate risks of gene drives and reduce uncertainty to the extent possible.	Our staged approach to the research and development process creates opportunities for dialogue and exchange, and iterative learning. Target Malaria will be working with external experts to define the plausible potential risks and identify sources of uncertainty at each stage, and use these discussions to design empirical studies, both in the lab and the field.
7. Engaging Communities, Stakeholders and Publics	
7-1: Research plans to develop gene drives should include a thoughtful engagement plan that considers relevant communities, stakeholders, and publics throughout the process of research, from proposal development through, if applicable, the release and monitoring of gene-drive modified organisms in the environment.	Engagement is a core activity for Target Malaria and is planned to take place throughout the research and development process. In addition to a global team, each of the Africa-based teams have a dedicated stakeholder engagement team of social scientists. The teams are currently engaging stakeholders at all levels from the local villages where entomological collections are being done, to the international level. The scope of their work will evolve to match the project's progress.
7-2: Because engagement can contribute to defining the values and preferences of communities, stakeholders, and publics about gene drive technologies, researchers and risk assessors should integrate engagement into the construction of risk assessment models. In turn, the outputs of risk assessments should feed back into engagement efforts.	Target Malaria considers engagement as a vital opportunity to receive feedback and help ensure the technology being developed meets the needs of potential beneficiary communities. The dialogue established through engagement is key to helping the teams understand possible risks and risk perceptions. The project will incorporate issues arising from its engagement into its internal risk analysis and the independent ecological risk assessments (starting with the release of non-driving sterile males), and into the design of the ecological relationships studies.

7-3: Funders of gene drive research should allocate a percentage of technical research grants' budgets to engagement activities, both to encourage good practice and to advance knowledge of effective engagement techniques.	Target Malaria strongly believes that any research project seeking to develop a technology for use in any country should have an engagement component built into its activities from its early stages. The project has permanent, full-time staff leading its engagement work and a dedicated multi-year budget from its core funding. The project is continuously seeking to expand its activities in this area and seeks additional funding sources to increase its capacity. In addition, the project's teams will share knowledge and experiences through publications in order to facilitate discussions, learning, and progress in the field as a whole.
7-4: Gene drive researchers should take a multi-disciplinary approach to engagement, partnering with social scientists, ethicists, evaluators, and practitioners with expertise in engagement to develop and implement engagement plans.	The complexity of the issues at hand in developing a new vector control tool require a multi-disciplinary team, not only in terms of scientific expertise but also in other areas. The engagement teams include people with a variety of backgrounds, including education in sociology, anthropology, political science, geography, and communications. Their experiences are also diverse, with a mix of academic researchers, NGO workers, public programmes implementers, and corporate sector experts. In addition, Target Malaria has established an Ethics Advisory Committee to provide external guidance to the project and contribute learnings from other fields. Members include individuals from four continents, with background in public health, biology, bioethics, and stakeholder engagement.
7-5: Researchers, funders, and policy makers should develop and implement plans to evaluate engagement activities related to gene drive research. When possible, these evaluations should be published in the scholarly literature or otherwise made available as part of a shared repository of knowledge.	Ongoing assessment and evaluation is built into the project through the work of our Ethics Advisory committee and as a built-in component of our engagement activities. At national and local level, engagement teams build feedback sessions into their workplans and regular internal audit of stakeholder engagement activities are scheduled to assess the effectiveness of current plans. The project also has a process for reporting incidents and leverages information garnered through that process to adjust and improve its engagement.

	The project is planning an external evaluation of its engagement activities in 2017, and we expect this will be repeated at regular intervals. Finally, as mentioned under 7.3 the teams are planning to publish in the literature as a means to share their experience and learnings once the engagement experience is sufficiently advanced.
7-6: Researchers, funders, and policy makers should adapt engagement plans that are relevant to the social, cultural, and political contexts in which gene drive research may be planned. This contextualization is especially important when the engagement process is organized or sponsored by groups and individuals whose origins and interests are different from those of the stakeholders, communities, or publics to be engaged. In such situations, particularly when field-testing or environmental release of gene-drive modified organisms are intended, it is critical to include local experts as partners in the design and implementation of the engagement process.	Co-development is core to Target Malaria's approach. Activities in Africa are led by three teams, located in Burkina Faso, Mali and Uganda. While we are many years away from testing a gene-drive product in Africa, the engagement teams in each country are already working with stakeholders to enable understanding of the project. Each engagement teams is composed of social scientists from the country, who are collaborating both with the scientific teams in their country and with other teams in the project.
7-7: Researchers, research institutions, and other organizers should explore ways to diversify engagement activities in order to include different voices at different times, especially given the intention for some gene-drive modified organisms to spread over time and across significant distances. Early in the development process, organizers should identify critical groups and time-points for interaction; as the research unfolds, these decisions should be revisited to ensure engagement activities remain appropriate and such related decisions should be revisited as the research unfolds.	Target Malaria has a dedicated team working on stakeholder engagement. The team does a careful stakeholder mapping to ensure that it engages with different voices and takes into account critical groups as well as more vulnerable groups or individuals for whom it might be difficult to have access to the public debate. This mapping is revisited frequently to take any changes into account. The project aims at having continuous engagement throughout the process and to check whether the acceptance level is maintained at all key steps of the research. In addition, the team proactively reaches out to other groups working on similar issues to discuss activities and strategies.

7-8: Researchers, research institutions, and other organizers should design engagement activities to respect different points of view. Such deliberation may enable participants to reflect upon their own beliefs and understandings in new ways. Dissent should be captured and considered carefully, but engagement does not require the dissenters to be convincing or convinced.	Target Malaria's engagement activities are focused on dialogue, and for that reason are planned to be carried out over multi-year timeframes so that stakeholders have the opportunity to reflect upon the project approach and intent. Starting engagement early in the research process is essential to allow for such deliberations to take place. While Target Malaria is several years away from possibly testing a gene drive-based construct in Africa, engagement has already been taking place for over two years in Burkina Faso, Mali and Uganda to accompany entomological activities and introduce the project. Engagement at national and international level is also underway. Target Malaria has implemented project-wide tools to help capture stakeholder inputs. All opinions, both positive and negative, are captured in a stakeholder engagement record, for the project to reflect on and to address. In addition, a specific mechanism has been implemented to collect stakeholder complaints or grievances in the three partner institutions. This mechanism provides a clear tool for accountability and allows stakeholders to express their discontent or any issue in a safe and transparent way.
8. Governing Gene Drive Research and Applications	
8-1: Institutions, funders, and professional societies should provide face-to-face instruction and online, open access resources for education and training on the responsible practices in gene drive research.	These recommendations are primarily directed at research institutes, funders, professional societies, and regulatory agencies. We agree with these recommendations and will be happy to work with these bodies on these issues.
8-2: Due to the novel characteristics of gene drives, funding agencies and research institutions should take responsibility to ensure the development of the necessary	

expertise to assess safety within Institutional Biosafety Committees and their equivalents.
8-3: Researchers and funders should take measures to review the study design and implementation on an ongoing basis to ensure that risks and benefits remain reasonably distributed and balanced.
8-4: The U.S. government should clarify the assignment of regulatory responsibilities for field releases of gene-drive modified organisms, including the roles of relevant agencies that are not currently included in the Coordinated Framework for the Regulation of Biotechnology.
8-5: Relevant agencies and decision making bodies will need to develop the capacity for robust assessment of a gene-drive modified organism's risks and uncertainties on a case-by-case basis that looks at the organism's intended function as well as the biological construct.
8-6: Regulatory agencies with oversight authority over genetic modification research should review risk assessment models and procedures to ensure that they capture the characteristics of gene drives, drawing upon multiple models and and integrating experts' comprehensive knowledge of practical conditions for gene drive research.
8-7: Researcher institutions, regulators, and funders should collaborate to develop oversight structures to regularly review the state of gene drive science and its potential for misuse. Such reviews should also recommend

or develop educational programs for researchers and members of the public about biosecurity concerns, the potential for dual-use research, responsible practices, and the funding of gene drive science.	
8-8: If field testing or environmental releases are expected to be conducted in other countries, United States funders and researchers should give careful consideration to the regulatory systems in place in those countries, their adequacy to control the development and release of gene-drive modified organisms, and the relevant community and other voices that will need to be considered in related governance.	
8-9: To ensure the long-term safety of human health and the environment, decision makers should consider a large toolbox of policies, including regulatory and non-regulatory mechanisms, for the rapidly developing field of gene drive research.	
8-10: Research institutions, regulators, and funders should revisit international regulatory frameworks, national laws, non-governmental policy, and professional codes of conduct on research and the release of genetically modified organisms to determine whether and how they may be applied to the specific context of gene drive research, particularly with regard to site selection issues, capacity building for responsible and inclusive governance systems, scientific and post release surveillance, and stakeholder engagement.	

9. Gene Drives on the Horizon: Overarching Considerations

9-1: Funders of gene drive research should coordinate, and if feasible collaborate, to reduce gaps in knowledge not only about the molecular biology of gene drives, but also in other areas of fundamental and applied research that will be crucial to the responsible development and application of gene drive technology, including population genetics, evolutionary biology, ecosystem dynamics, modelling, ecological risk assessment, and public engagement.	Agreed: all of these are key disciplines for the proper development and assessment of gene drive interventions, and further funding and collaboration to support these activities would be welcome.
9-2: Funders of gene drive research should establish open access, online repositories of data on gene drives as well as standard operating procedures for gene drive research to share knowledge, improve frameworks for ecological risk assessment, and guide research design and monitoring standards around the world.	As a not-for-profit research and development consortium we are committed to publishing our results, and the methods and protocols used to obtain them. Publications by the team are listed on our website and can be accessed online.
9-3: The distinguishing characteristics of gene drives—including their intentional spread and the potential irreversibility of their environmental effects—should be used to frame the societal appraisal of the technology, and they should be considered in ecological risk assessment, public engagement, regulatory reform, and decision making.	As outlined in sections 6 and 7, our project has both risk analysis and stakeholder engagement as integral components of its work. We actively work with other relevant groups to ensure integration.
9-4: Proposed field tests or environmental releases of gene-drive modified organisms should be subject to an ecological risk assessment and structured decision making processes. These processes should include modelling of off-target and non-target effects from the	Even though Target Malaria is many years from open releases of a gene drive construct, it has sought an independent quantitative risk assessment for a much earlier phase of our research (maintenance of a male-sterile strain in containment), and will continue to solicit such assessments with subsequent phases up to release of a driving construct. These will expand

genome level through ecosystem level. When possible, empirical estimates of such variables as gene flow, population change, trophic interactions, and community dynamics should be developed as part of the models.	in scope to include off-target and non-target effects. Moreover, we are currently developing a research programme to collect the ecological data that will be needed for the assessments (including gene flow, population change, tropic interactions, and community dynamics).
9-5: Governing authorities, including research institutions, funders, and regulators, should develop and maintain clear policies and mechanisms for how public engagement will factor into research, ecological risk assessments, and public policy decisions about gene drives. Defined mechanisms and avenues for such engagement should be built into the risk assessment and decision-making processes from the beginning.	Target Malaria is taking public input into account in its research, for example by expanding its work to address questions about environmental interactions. We are also incorporating questions expressed by the communities into risk assessments.
9-6: In selecting sites for field testing and environmental releases, researchers and funders should be guided by their professional judgement, the feasibility of risk assessment and community engagement, and the community's values and understanding of the balance of benefits and harms. In site selection, preference should be given to locations in countries with the existing scientific capacity and governance frameworks to conduct and oversee the safe investigation of gene drives and development of gene-drive modified organisms.	Target Malaria brings together teams based in Africa, North America and Europe. Each of the African countries currently participating in Target Malaria were selected on the basis of their expertise and taking into consideration the context in which they operate. All have good scientific capacity; a regulatory framework for dealing with genetically modified organisms; and a political desire to confront the burden of malaria.