GUIDANCE FRAMEWORK FOR TESTING **GENETICALLY MODIFIED MOSQUITOES**

Second edition

World Health Organization

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GUIDANCE FRAMEWORK FOR TESTING **GENETICALLY MODIFIED MOSQUITOES**

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Foreword

Dr Soumya Swaminathan
Chief Scientist &
WHO Special Coordinator for TDR
World Health Organization

Vector-borne diseases are endemic in more than 100 countries and affect approximately half of the world's population *(1)*. Many types of arthropods may serve as disease vectors, but this guidance focuses particularly on mosquitoes. Mosquitoes transmit several diseases of major global public health importance, including malaria and dengue fever *(1)*. In fact, mosquitoes have been called the deadliest animal on earth *(2)*.

Malaria is still considered the world's most important parasitic infectious disease. Intensive deployment of currently available malaria control tools over the past two decades has greatly reduced malaria incidence *(3)*. However, this overall trend has slowed in recent years, and even reversed in some parts of Africa *(4, 5)*. The *Global technical strategy for malaria 2016–2030 (6)* sets a target of reducing global malaria incidence and mortality rates by at least 90% by 2030 (compared to 2015 levels). Yet, it is widely acknowledged that eliminating malaria in all countries, especially those with a high disease burden, will likely require new tools that are not available today *(6–8)*. Therefore, investing in research and development of innovative vector control tools has been identified as a priority *(9)*.

An estimated 2.5 billion people live in areas where dengue viruses can be transmitted. Dengue has been called the most important mosquito-borne viral disease with epidemic potential in the world, citing a 30-fold increase in the global incidence of dengue over the past 50 years, and recognizing that the human and economic costs are staggering. The number of cases reported increased from 2.2 million in 2010 to over 3.34 million in 2016 *(10)*. Outbreaks and epidemics of other viruses carried by the same mosquitoes that transmit dengue have occurred in Africa, the Americas, Asia and the Pacific *(1, 11)*.

Attacking mosquito vectors is one of the most effective ways to reduce the transmission of these diseases in endemic areas *(12)*. Application of mosquito population reduction methods was central to the successful elimination of malaria transmission in Italy and the United States of America in the early 20th century *(13)* and, transiently, of dengue in the Americas in the early 1960s *(14)*. Vector-targeted approaches remain a mainstay of current disease control practices. However, given the

magnitude of ongoing malaria and dengue incidence, current efforts clearly are insufficient to meet the need. Moreover, dependence on a limited number of insecticides for vector control increases the risk that mosquitoes will develop resistance *(15)*, exacerbating the problem. Insecticide resistance is being reported in over three quarters of countries with ongoing malaria transmission, and such resistance affects all major vector species and classes of insecticide *(7)*. Resistance to all four classes of insecticide has also been reported in *Aedes* arbovirus vectors in the Americas, Asia and Africa *(16)*.

In considering the potential of new technologies to address the unmet needs of mosquito control, it is necessary to evaluate the benefits and risks in the context of the current situation. The potential public health benefit of practical and effective new tools to reduce or even eliminate diseases such as malaria and dengue is clear and widely recognized *(17)*. Both the risks incurred by testing new and unproven control strategies and the risks to human health and the environment posed by maintaining the status quo, which include ongoing health (morbidity and mortality), environmental (use of broad-spectrum insecticides) and economic *(18–20)* impacts, should be taken into account in decision-making.

For more than two decades, scientists have been working to harness the promise of molecular biology to develop genetically modified mosquitoes (GMMs) for use as public health tools to prevent the transmission of these diseases. The introduction of molecular biology techniques represents the next step in a progression that builds on the widespread success of programmes employing release of radiation-sterilized insects to control the Mediterranean fruit fly (Medfly) and other insect pests affecting plants and animals, a process known as the sterile insect technique (SIT) *(21)*. Radiation- and chemo-sterilization, sometimes in combination with biological sterilization methods, have been applied to mosquitoes *(22–24)*. However, genetic modification technologies offer additional options for specificity and durability of effect, as well as adaptability to different disease transmission conditions. Advances in the development of GMMs have raised hopes for the availability of new, potent and cost-effective tools to aid in the fight against malaria, dengue and other mosquito-borne pathogens. Data on which to base the evaluation of GMMs' protective potential can only be collected through testing, including testing under the natural conditions in which the technology would be utilized. Without the ability to conduct careful and rigorous testing, no new technology of any kind can be brought to fruition for the public good.

Some of these genetic technologies are now advancing to field testing. Field testing of GMMs began with releases of non-replicating male mosquitoes (which do not bite) *(25–27)*. The first field release of non-sterile, self-limiting GMMs was announced in 2019 *(28)*. To date, no gene drive-modified mosquitoes (GDMMs)[1] have been tested in the field. Given the novelty of GMMs, and particularly GDMMs, concerns have been raised in a number of forums about the need for thorough, thoughtful and transparent preparation for and conduct of field trials. Frameworks for risk assessment and regulation have been produced at various levels (reviewed in Sections 3 and 5 of this guidance).

As the research progresses, a need has been expressed, both within the scientific community and by the public, for additional standards and guidance. The Special Programme for Research and Training in Tropical Diseases of the World Health Organization (WHO-TDR) and the Foundation

[1] GMMs are defined here as mosquitoes that have traits derived through the use of recombinant DNA technology (see Glossary), and thus GDMMs refer to mosquitoes modified with engineered gene drive systems.

for the National Institutes of Health (FNIH) co-sponsored a technical consultation meeting in 2009 to assess the current progress and future development of GMM technologies. The meeting was attended by an international group of participants with expertise in molecular biology, medical entomology, ecology, regulatory requirements, and ethical, social and cultural issues, as well as staff from WHO, FNIH and other research funders *(29)*. Participants recommended that WHO and FNIH establish a working group to develop a comprehensive guidance framework to provide quality standards for assessing the safety and efficacy of GMMs and addressing legal, ethical, social and cultural issues that may arise during their development and deployment. A subsequent multidisciplinary, multiyear effort was commissioned, resulting in the publication of the first WHO *Guidance framework for testing genetically modified mosquitoes* in 2014 *(30)*. Because of the breadth of potential genetic approaches and conditions under which they might be used, the 2014 *Guidance framework* did not offer precise instructions for testing GMMs, but aimed to support informed and thoughtful process development. Best practices for efficacy and safety testing were proposed that complement those used for trials of other new public health tools, including drugs, vaccines and insecticides, and draw also from relevant experience in agriculture and biocontrol. The 2014 *Guidance framework* examined fundamental considerations for addressing public engagement and transparency needs in GMM research, taking into account lessons learned from previous introductions of new technologies in the fields of health and agriculture. It also reviewed existing regulatory requirements and guidance that were either directly pertinent to research on GMMs or were considered to provide precedents for establishing the appropriate level of oversight. Best practices set forth in the 2014 *Guidance framework* have had broad influence on the thinking about the research and development of GMMs and GDMMs *(31–34)*.

The *Guidance framework* was envisioned as a living document, to be updated as necessary to keep pace with the research on GMMs and GDMMs. This revised version of the *Guidance framework for testing of genetically modified mosquitoes* takes into account the technical progress made and lessons learned since 2014 in this rapidly advancing field of research. Like the original *Guidance framework*, it is intended to provide standards that foster quality and consistency in the processes for developing, testing and regulating these new genetic technologies. Best practices recommended in the 2021 *Guidance framework* will further contribute to the comparability of results and credibility of conclusions in order to facilitate decision-making by countries interested in the potential use of GMMs as public health tools for the control of vector-borne diseases.

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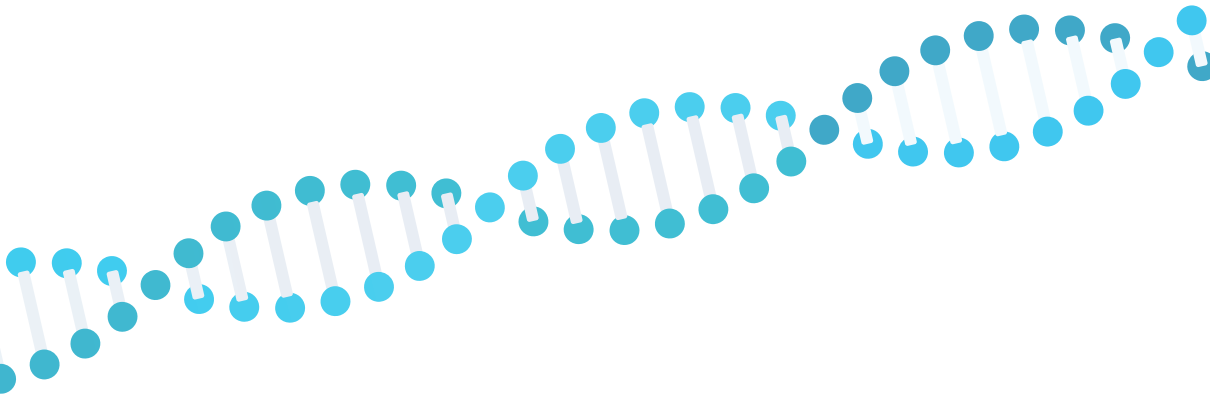

Acknowledgements

2021 contributors

Core Working Group: *These individuals were substantively involved in writing, compiling and editing the guidance framework.*

Mark Benedict* (Centers for Disease Control and Prevention), Brinda Dass* (Foundation for the National Institutes of Health); Claudia Emerson* (McMaster University), Stephanie James* (Foundation for the National Institutes of Health), Hector Quemada* (Western Michigan University), Travis Ramsay* (McMaster University), Willy Tonui* (Environmental Health and Safety Consultancy Ltd.)

Contributors: *These individuals were consulted for information and advice during the development of the draft guidance framework.*

Vibha Ahuja* (Biotech Consortium India Ltd.), Luke Alphey* (The Pirbright Institute), Paulo Paes de Andrade* (TargetDNA Biosafety Consultancy), Camilla Beech*≠ (Cambea Consulting Ltd.), Steve Lindsay‡ (Durham University), John Mumford* (Imperial College London), David O'Brochta* (Foundation for the National Institutes of Health), Aaron Roberts* (McMaster University)

External reviewers: *These individuals provided comments on the draft guidance framework.*

Abdoulaye Diabate (Institut de Recherche en Sciences de la Santé, Bobo-Dioulasso, Burkina Faso), Austin Burt (Imperial College London), Boet Glandorf (National Institute of Public Health and the Environment, Bilthoven, The Netherlands), Cameron Simmons (Monash University, Melbourne, Australia), Charles Mbogo (KEMRI-Wellcome Trust Research Programme, Nairobi, Kenya), Christophe Boete (Université de Montpellier, France), Damaris Matoke (Kenya Medical Research Institute, Nairobi, Kenya), Florencia Luna (Facultad Latinoamericana de Ciencias Sociales, Ciudad Autónoma de Buenos Aires, Argentina), Fred Gould (NC State University, Raleigh, USA), Jeremy Bouyer (International Atomic Energy Agency, Seibersdorf, Autriche), Jeremy Ouedraogo (African Biosafety Network of Expertise, Dakar, Senegal), Joseph Mfutso-Mbengo (University of Malawi, Blantyre, Malawi), Mutibo Chijikwa-Mushenywa (National Biosafety Authority, Lusaka, Zambia), Paulo Andrade (Universidade Federal de Campina Grande, Patos, PB, Brazil), Peter Smith (London School of Hygiene and Tropical Medicine, London, UK), Tony Nolan (Liverpool School of Tropical Medicine, Liverpool, UK), Yeya Toure (Retired Professor and researcher, Bamako, Mali)

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2014 contributors

Core Working Group: *These individuals were substantively involved in writing, compiling and editing the guidance framework.*

Mark Benedict* (University of Perugia), Mike Bonsall* (University of Oxford), Anthony A. James* (University of California, Irvine), Stephanie James* (Foundation for the National Institutes of Health), Jim Lavery* (St. Michael's Hospital and Joint Centre for Bioethics); John Mumford* (Imperial College London), Hector Quemada* (Donald Danforth Plant Science Center), Robert Rose*, Paul Thompson‡ (Michigan State University) Yeya Toure‡ (Special Programme for Research and Training in Tropical Diseases, WHO-TDR), Guiyun Yan‡ (University of California, Irvine).

Contributors: *These individuals were consulted for information and advice during the development of the draft guidance framework.*

Luke Alphey≠* (Oxitec Ltd.), Nina Alphey≠ (University of Oxford), Jeff Bale¥ (University of Birmingham), Henk Braig‡ (Bangor University), Paul De Barro* (Commonwealth Scientific and Industrial Research Organization), Stephen Dobson‡ (University of Kentucky), Andrew Githeko‡ (Kenya Medical Research Institute), Charles Godfray* (University of Oxford), Fred Gould* (North Carolina State University), Steven Juliano‡ (Illinois State University), Pattamaporn Kittayapong‡ (Mahidol University), Bart Knols* (In2Care BV, the Netherlands), Christian Lengeler‡ (Swiss Tropical and Public Health Research Institute), Mauro Marrelli‡ (University of Sao Paulo), John Marshall‡ (Imperial College, London), Darlene McNaughton‡ (Flinders University), Scott O'Neill‡ (Monash University), Malla Rao‡ (National Institute of Allergy and Infectious Diseases, National Institutes of Health), Janine Ramsey-Willoquet‡ (Instituto Nacional de Salud Pública, Tapachula), Steven Sait* (University of Leeds), Thomas W. Scott* (University of California, Davis), Charles Taylor‡ (University of California, Los Angeles), Steven White‡ (Centre for Ecology and Hydrology, the United Kingdom), Bin Zheng‡ (Chinese Center for Disease Control).

External reviewers: *These individuals provided comments on the draft guidance framework prior to the public comment period.*

Margareth Capurro* (University of Sao Paulo), Adriana Costero-Saint Denis* (National Institute of Allergy and Infectious Diseases, National Institutes of Health), AP Dash‡ (WHO SE Asian Regional Office), Jeremy Farrar‡ (Oxford University Clinical Research Unit, Viet Nam), Jeffrey Hii‡ (WHO Western Pacific Regional Office), Wen Kilama¥ (African Malaria Network Trust), Louise Malone‡ (New Zealand Institute for Plant and Food Research), Charles Mbogo‡ (Kenya Medical Research Institute), Stuart Pimm‡ (Duke University), David Resnik‡ (National Institute of Environmental Health Sciences, National Institutes of Health), Johannes Sommerfeld‡ (Special Programme for Research and Training in Tropical Diseases, WHO-TDR), Max Suckling‡ (New Zealand Institute for Plant and Food Research), Jeff Waage‡ (London International Development Center).

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* Self-identified a professional interest in GMMs.
‡ Self-identified neither a professional nor a commercial interest in GMMs.
≠ Self-identified a commercial interest in GMMs.
¥ Could not be reached in 2014.

Abbreviations

APHIS	USDA Animal and Plant Health Inspection Service
BCH	Biosafety Clearing-House
CBD	Convention on Biological Diversity
CPB	Cartagena Protocol on Biodiversity
CSO	civil society organization
DSMB	Data and Safety Monitoring Board
EFSA	European Food Safety Authority
EIR	entomological inoculation rate
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FDA	US Food and Drug Administration
FNIH	Foundation for the National Institutes of Health
FPIC	Free, Prior and Informed Consent
GCP	Good Clinical Practice
GDMM	gene drive-modified mosquito
GMM	genetically modified mosquito
GMO	genetically modified organism
GPS	Global Positioning System
HT	horizontal transfer
IA	impact assessment
IAPSC	Inter-African Phytosanitary Council
IBC	institutional biosafety committee
ICCPR	International Covenant on Civil and Political Rights
ICH	International Council for Harmonisation
IEC	institutional ethics committee
IIBC	International Institute of Biological Control

Abbreviations

IITA	International Institute of Tropical Agriculture
IPPC	International Plant Protection Convention
IRS	indoor residual spraying
ISPM	International Standards for Phytosanitary Measures
ITN	insecticide-treated net
IVM	integrated vector management
LMO	living modified organism
NASEM	National Academies of Science, Engineering and Medicine
NBA	national biosafety authority
NEPA	National Environmental Policy Act
NEPAD	New Partnership for Africa's Development
NTO	non-target organism
RA	risk assessment
RDT	rapid diagnostic test
RM	risk management
SDG	Sustainable Development Goal
SIT	sterile insect technique
SOP	standard operating procedure
UD	underdominance
USA	United States of America
WHO	World Health Organization
WHO-TDR	Special Programme for Research and Training in Tropical Diseases of the World Health Organization
WTO	World Trade Organization

Glossary

Alleles – different forms of the same gene.

Area-wide control – methods of reducing pest damage, the effectiveness of which depends on application over large expanses. This contrasts particularly with personal protection, for example, as provided by insecticide-treated nets and repellents.

Autosome – any chromosome (structure composed of DNA and protein that carries genetic information) that is not a sex-determining chromosome.

Biosafety committee – group responsible for implementing policies and guidelines related to the use of potentially hazardous biological agents, including but not limited to infectious agents, human materials, and recombinant DNA studies. This group ensures that research involving these agents does not endanger researchers, laboratory workers, human research subjects, the public or the environment.

Cartagena Protocol on Biosafety – an international agreement dealing with the safe handling, transport and use of living modified organisms (LMOs) resulting from modern biotechnology. See: http://bch.cbd.int/protocol/

Clinical disease incidence – the number of new clinical cases per unit of time for the at-risk population. This is typically determined by voluntary reporting of symptoms or community-based active case detection followed by a laboratory diagnostic test.

Cluster randomized trials – trials that group individuals into clusters, such as residents of particular villages or urban neighbourhoods. Each cluster is assigned randomly an experimental treatment such as a placebo or drug, or, in the case of genetically modified mosquitoes (GMMs), releases may be in one set of clusters and not in another.

Community engagement – practices undertaken to inform stakeholders about the diseases and vectors of interest and goals of a proposed research study or intervention trial, and to understand their perspectives and reaction.

Confinement – utilization of measures that seek to prevent unplanned or uncontrolled release of organisms into the environment. This may involve physical confinement (sometimes termed "containment") within a large cage that simulates the disease-endemic setting while minimizing the possibility of escape, and/or ecological confinement by geographical/spatial and/or climatic isolation.

Data and Safety Monitoring Board – a committee of experts independent of the organization conducting a clinical trial, which monitors trial progress, reviews safety and effectiveness data while the trial is ongoing, and can recommend the trial be stopped early because of concerns about participant safety or because the research question has been answered.

Declaration of Helsinki – a set of ethical principles for the medical community regarding human experimentation, issued by the World Medical Association.

Deployment – implementation of GMM technology as part of a national or regional programme for vector control.

Dispersal – movement of mosquitoes into a different habitat.

Drive (also called gene drive) – a mechanism that increases the transmission of a transgene in a population above that which would be expected based on Mendelian inheritance. The increase is reflected in the excess proportion of progeny that carry the transgene.

Ecosystem – a biological system composed of a community of organisms and the nonliving environment with which it interacts.

Endemic – a situation in which disease is present continuously at some level in an area.

Endonuclease – an enzyme that cleaves the bond between two components of a nucleic acid such as DNA or RNA.

Endpoint – an event or outcome that can be measured objectively to determine whether the intervention being studied has the desired effect.

Entomological inoculation rate (EIR) – a measure of the degree of infection risk that a human population is exposed to for a particular disease, as determined by assessing the vector mosquito population. It is described by the frequency of infectious mosquitoes feeding upon a person within some unit of time, such as per day or year.

Epidemic – an increase in incidence and prevalence of disease affecting many people rapidly and extensively and above normal levels in an area, but not continuously present at such levels.

Ethics – an activity or inquiry intended to shed light on the correctness or justifiability of a given course of conduct.

Ethics committee (also called institutional ethics committee, institutional review board or ethical review board) – a group charged with providing oversight of biomedical and behavioural research involving humans, with the aim to protect the rights and welfare of research subjects.

Fitness – description of the ability to both survive and reproduce, equal to the long-term average contribution to the gene pool by individuals having a particular genotype or phenotype. If differences between alleles of a given gene affect fitness, then the frequencies of the alleles will change over generations, with the alleles with higher fitness becoming more common.

Fixation – a change in the gene pool whereby one variant of a gene becomes established at 100% frequency in the population.

Frequency – an expression of how common a particular gene variant is in the population.

Gene – a segment of DNA that contains information required by cells for synthesis of a product.

Gene flow – the movement (expressed as increase in frequency) of genes or alleles into a population from one or more other populations.

Genetically modified mosquitoes (GMMs) (also called genetically engineered mosquitoes, transgenic mosquitoes, or living modified mosquitoes) – mosquitoes that have heritable traits derived through the use of recombinant DNA technology, which alter the strain, line or colony in a manner usually intended to result in reduction of the transmission of mosquito-borne human diseases – see also Genetically modified organism. GMMs are also likely to be characterized by introduced heritable marker traits to facilitate monitoring upon release into the environment and, in some cases, may include only such markers, as for population biology studies.

Genetically modified organism (GMO) (also called living modified organism) – any organism that has in its genome novel DNA of endogenous, exogenous or mixed origin that was made using modern recombinant DNA technology. Although successive selective breeding of strains of organisms with naturally occurring allelic variations also results in strains with genotypes that differ from the natural population, these are excluded from this definition.

Genotype – the genetic constitution of an organism.

GMM system – a transgenic construct incorporated into a mosquito.

Good Clinical Practice (GCP) – an international quality standard for trials involving human subjects, including protection of human rights, assurance of safety and efficacy, and standards on conduct of clinical trials. See: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC5000 02874.pdf

Hazard – an event, activity or other cause of a negative consequence or impact identified in a risk analysis.

Horizontal gene transfer (HGT) – heritable transfer of a functional genetic element from one organism to another without mating, most often relating to genetic exchange between different species.

Infection incidence – the rate at which new infections occur during a specific period of time.

Informed consent – the process intended to ensure that human subjects who will be observed or involved in a research activity are fully and explicitly advised of all risks, costs or inconveniences they may bear as a result of participating as a research subject, and voluntarily agree to accept or bear those risks and costs.

Integrated vector management (IVM) – rational decision-making for optimal use of resources for vector control. The aim is to improve the efficacy, cost-effectiveness, ecological soundness and sustainability of vector control activities against vector-borne diseases.

Introgression – the transfer of genetic material from one organism to another through hybridization.

Localizing – approaches in which the distribution of the modification is intended to be spatially restricted.

Mark-release-recapture – a method used to estimate the population size of free-living animals, including mosquitoes, and to study population survival and dispersal in space and time. A portion of the mosquito population under study is captured, marked (usually with fluorescent powders) and released. A portion of the population into which they were released is captured later and the number of marked mosquitoes within the sample is counted. The proportion of marked mosquitoes in the second sample enables estimation of the total number of animals in the whole population.

Non-localizing – approaches in which the modification is intended to distribute widely within interbreeding populations.

Non-target organism – any organism that is not a direct target of an intended intervention. For GMMs, the direct target organism is other mosquitoes of the same species in the wild population.

Nuremberg Code – an ethics code that serves as a basis for bioethical principles ensuring the rights of human subjects in medical research.

Off-target effects – the outcomes of actions that are not directed to the purpose of the action, whether anticipated or not, possibly affecting either target or non-target organisms. Off-target effects may have negative, neutral or positive impacts on the intended purpose.

Pathogen – an organism that causes disease. In dengue infection, the pathogen is a virus. In malaria infection, the pathogen is a unicellular parasite.

Penetrance – the frequency at which a trait is expressed in individuals carrying a particular gene associated with the trait.

Persistence – a descriptor of how long the genetic modification system remains effective.

Pharmacovigilance – the process of collecting, monitoring, researching, assessing and evaluating information on the long-term adverse effects of medicines.

Phenotype – the observable characteristics of an organism, based on genetic and environmental influences.

Population regulation – maintenance of a population around or near an equilibrium level, such as by density-dependent factors.

Population replacement (also called population modification, population alteration or population conversion) – strategies that target vector competence with the intent to reduce the inherent ability of individual mosquitoes to transmit a given pathogen.

Population suppression (also called population reduction) – strategies that target vector density with the intent to reduce (suppress) the size of the natural mosquito population to the extent that it would not be able to sustain pathogen transmission.

Prevalence of infection – the frequency of infection within a population at any given time.

Refractoriness – a condition in which the mosquito is intrinsically unable to support the development of a pathogen to an infective stage or to a point of sufficient abundance such that the mosquito cannot transmit disease.

Regulation – an official rule to manage the conduct of those to whom it applies, usually developed from legal interpretations of legislation and implemented by government ministries or agencies.

Regulatory agency (also called regulatory authority, ministry, regulatory body, or regulator) – a public authority or government entity responsible for exercising authority over some area of activity in a supervisory capacity.

Risk – an objective measure of the product of the likelihood and consequences of a hazard, defined within a prescribed set of circumstances. Risk is often described as a probability distribution of a set of consequences over a defined time period.

Risk analysis – the process of risk identification, risk assessment, risk management and risk communication.

Risk assessment – a methodological approach to define and characterize hazards, and to estimate the exposure or likelihood of each hazard occurring, as well as the potential adverse impact of the hazard (harm).

Risk communication – the process through which risk concerns and risk tolerance are articulated by relevant stakeholders and the results of risk assessment and risk management are communicated to decision-makers and the public.

Risk management – the process of identifying and implementing measures that can be expected to reduce risk to an acceptable level.

Self-limiting – GMM approaches in which the genetic modification will not pass on indefinitely through subsequent generations.

Self-sustaining (also called self-propagating or self-perpetuating) – GMM approaches in which the heritable modification is spread and maintained indefinitely through the target population.

Semi-field testing – studies conducted under physical confinement in an outdoor cage facility.

Spread – transmission of the genetic modification system to other individuals within an interbreeding population.

Sterile insect technique (SIT) – the inundative release of factory-produced sexually sterile insects into wild native insect populations so that there is a high ratio of sterile males to wild females. Sterilization is usually accomplished using radiation or chemicals. The effect is population suppression, and the effort is most effective when continual and over large areas to reduce the effects of fertile immigrants. Release only of males is preferred, although release of both sexes has also been effective. SIT has been applied most widely against agricultural pests.

Threshold – the proportion of GMMs, with respect to the total population of the target mosquito species, that will reliably initiate establishment and spread of the modification to high frequency by mating.

Traits – phenotypes that result from single or multiple genes and their interactions with the environment.

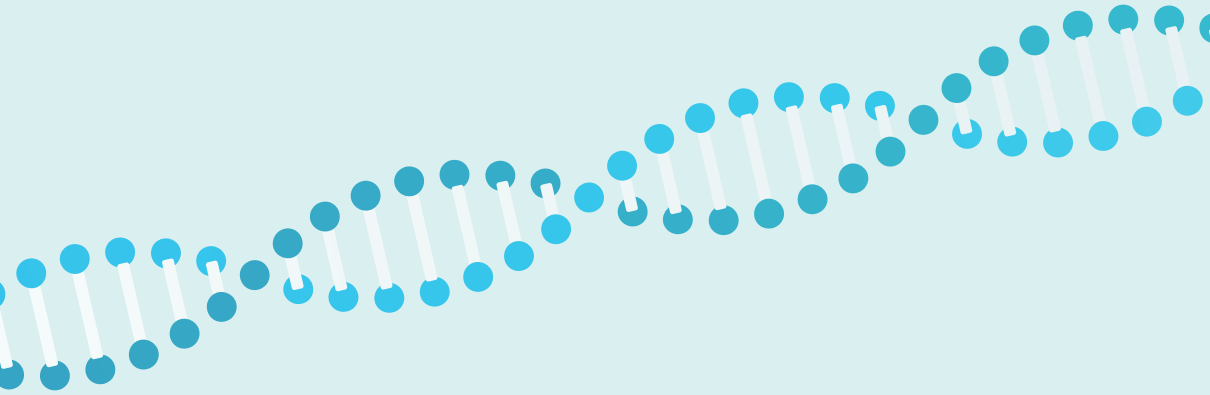
Transboundary movement – movement across national, state or other political lines of demarcation.

Transgenic construct – a piece of DNA that has been integrated into the genome of the recipient organisms, typically consisting of a promoter and/or enhancer to provide the desired spatial and temporal pattern of transgene expression, one or more genes to be transcribed, and sequence to stop transcription.

Vector competence – the ability of a vector to become infected with, maintain and transmit a pathogen.

Vector mosquitoes – mosquitoes that are able to transmit a disease-causing pathogen.

Vectorial capacity – a description of the potential for a vector to transmit a pathogen, taking into account vector survival and biting rate, ratio of mosquitoes to human or animal hosts, and the period of time between when the vector ingests the pathogen and when it becomes infectious for a new host.



Executive summary

Despite ongoing control efforts, diseases transmitted by mosquitoes, such as malaria and dengue, continue to be an enormous global health burden. There is broad recognition of the need for improved tools to combat these diseases, including tools for vector control and prevention of disease transmission.

Currently available methods to control mosquito vectors are based on the use of insecticides and elimination of mosquito larval breeding sites. In considering the potential of new technologies to address the unmet needs of mosquito control, it is necessary to evaluate their risks and benefits in the context of the current situation. Therefore, the risks incurred by testing new and unproven strategies should be weighed against the risks to human health and the environment posed by maintaining the status quo, which includes both ongoing disease and insecticide exposure, and by changing factors affecting mosquito abundance, such as land use and urbanization.

Genetically modified mosquitoes (GMMs) have been proposed as new tools to reduce the transmission of diseases such as malaria and dengue. This *Guidance framework* is intended to foster the quality and consistency of procedures for testing GMMs, which will contribute to the comparability of results and credibility of conclusions to support decision-making by those considering the use of GMMs as public health tools to control mosquito-borne diseases. The *Guidance framework* should be useful to readers interested in:

- GMM technologies and applications that are currently being tested or contemplated;
- safety, efficacy, regulatory and social/ethical issues involved in taking GMMs from the laboratory to field testing and implementation;
- precedents for how similar issues have been dealt with to date; and
- existing regulatory frameworks and international agreements relevant to the testing and eventual implementation of GMMs.

GMM technologies

GMM strategies currently under development are aimed at either reducing the size of the mosquito vector population to an extent that will significantly decrease pathogen transmission ("population suppression") or modifying the native mosquito population to make it less capable of transmitting a particular pathogen ("population replacement").

These technologies can be further defined according to how long the GMMs are intended to persist following release and how extensively the modification is intended to spread within the targeted mosquito population. Characteristics of persistence and spread will depend on the transgenic components and their behaviour, including whether they incorporate a drive mechanism that will increase the likelihood that the modification will be inherited (gene drive-modified mosquitoes [GDMMs]), as well as the circumstances of the GMM use.

- With "self-limiting" approaches, the genetic modification is designed to decline in frequency within the mosquito population over time. In some cases, the GMMs are meant to be sterile and thus entirely unable to pass the genetic modification to future generations through mating. In other cases, the GMMs are meant to mate and introduce the effect transiently into the local mosquito population, but the frequency of the modification is expected to be reduced over time. Thus, the protective effect of self-limiting approaches can only be maintained by periodic re-releases of GMMs. How often these releases must be performed will depend on the type of genetic modification. From a risk assessment perspective, these releases can be readily halted and this should decrease the risk of producing long-term undesirable changes in the environment. However, the need for frequent reintroductions is associated with ongoing cost and complexity of production and delivery.
- With "self-sustaining" approaches, the genetic modification is intended to spread to interbreeding populations of the targeted mosquito species and persist indefinitely. The extent of persistence will be influenced by whether the GMM strategy aims for population suppression or replacement. These approaches have the potential to provide highly durable and cost-effective protection against pathogen transmission, but any unforeseen effects would be more difficult to reverse than with self-limiting approaches.

GMM technologies can also be categorized according to how far they are expected to spread and disperse in the environment. "Localizing" approaches are intended to remain spatially restricted around the area of release, whereas "non-localizing" approaches are intended to distribute widely among interbreeding populations. The extent of spatial spread will be influenced by persistence characteristics.

GMM technologies can be used in ways that are compatible with other disease control methods and could be incorporated into integrated vector management (IVM) programmes. GMM technologies offer several theoretical advantages in disease control and elimination efforts.

- They may reach mosquito populations and mosquito larval breeding sites that have traditionally been the most difficult and expensive to access with conventional tools, by exploiting the natural behaviour of mosquitoes to mate and seek sites for egg-laying. For example, GMMs would be well-suited to urban settings, where current control measures are often ineffective due to the wide availability of cryptic mosquito larval breeding sites.

Additionally, GMMs may reach outdoor and day-biting mosquitoes that escape control methods such as insecticide-treated nets (ITNs) and indoor residual spraying (IRS).

- The modification could be made highly specific for the targeted mosquito species, which would avoid the ecological and environmental hazards associated with commonly used broad-spectrum insecticides.
- GMMs could provide continuous protection in situations where other disease control methods have been interrupted, and prevent the reintroduction of the pathogen after successful elimination efforts. The protective effect of GMMs would not be dependent upon socioeconomic status and would not place additional burdens, such as the need for behaviour change, on people living in the treated area.

Theoretical disadvantages have also been raised for GMMs, including uncertainties related to possible ecosystem interactions and concerns over appropriate governance.

Because of the breadth of different genetic approaches that are under consideration and the broad range of conditions under which they might be used, it is not possible to provide a universal formula for evaluating GMM technologies. As with other public health tools, case-specific testing will be required to understand the advantages and disadvantages of a particular GMM approach, keeping in mind both the potential benefits and risks. This can begin prior to field testing as particular GMM systems are developed, building on principles already described for existing technologies. A phased testing pathway is recommended for GMMs, analogous to the development pathway for other new public health tools, with systematic iterative assessment of safety and efficacy. The transition from one phase to the next will be subject to decision criteria, including efficacy and safety endpoints, regulatory and ethical approvals, and social acceptance.

- New GMM technologies would first move from the laboratory or other indoor facility (Phase 1) to testing under conditions that provide a more natural setting but still limit release into the environment (Phase 2).
- Phase 2 may involve testing under physical confinement, as in a large outdoor cage within a disease-endemic setting, or releases under ecological or geographical conditions intended to limit mosquito migration. This testing will primarily examine whether the GMMs' function observed in Phase 1 is maintained under more natural conditions. The needs for confined testing will be informed by risk assessment and prior experience with the technology.
- GMMs may then proceed through a series of staged open release trials in Phase 3 designed to measure performance under different conditions; this will include measurement of their efficacy for preventing infection or disease.
- Based on the results from Phase 3, a decision may be made to implement GMMs as a public health intervention. Phase 4 would be accompanied by ongoing monitoring of safety and effectiveness following implementation.
- For self-sustaining, non-localizing GDMMs, testing in a series of discrete phases may not be possible after Phase 1, but rather may be undertaken as a sequence of expanding releases. Therefore, safety testing in Phase 1 and thorough risk assessment prior to Phase 2 will be especially important for these GDMMs.

The critical path for GMM development will include not only proof of efficacy, but also proof of acceptability and deliverability. Risk analysis, community and other stakeholder engagement, and regulatory approval all contribute to determination of acceptability. Cost-effectiveness of the technology in relation to other available disease control methods may influence acceptability. Deliverability will require an operating model with appropriate prospects for financing to support implementation and subsequent monitoring, sufficient technical and production capacity, quality control processes, capability to provide appropriate mitigation or remediation in the case of unforeseen effects, and commitment to ongoing stakeholder engagement.

Efficacy evaluation

GMMs must be effective in reducing transmission of the targeted pathogen(s) and if they are used as public health interventions. Demonstration of efficacy will be a critical determinant for decision-making about implementation. The efficacy of GMMs may be measured using both entomological and epidemiological endpoints. The entomological endpoint is a reduction in the risk of disease transmission as measured by specific mosquito population characteristics. The epidemiological endpoint is a reduction in the incidence or prevalence of infection or disease in human populations. Whereas entomological endpoints may be relevant through all phases of testing, epidemiologic endpoints are expected to become measurable only when research progresses to large-scale field releases. Entomological endpoints should be established with the eventual epidemiological goal in mind.

Because direct measurement of a reduction in transmission intensity will be difficult during early testing, it will be useful to identify surrogate indicators of entomological efficacy, i.e., characteristics that contribute to transmission intensity such as vector population size, GMM fitness, pathogen replication within the GMMs, and transgene frequency.

Trials to assess epidemiological efficacy must be designed to enable measurable reductions in the incidence or prevalence of infection or disease. Trial design must take into account the functional characteristics of the GMMs, which for GDMMs will include the rate at which the modification spreads into the local mosquito population, as well as field site characteristics. “Go” and “no-go” criteria for moving forward to the next stage of testing should be established. Independent monitoring of trials is recommended at all phases, but trials for epidemiological efficacy will require an independent Data and Safety Monitoring Board (DSMB).

Careful site selection will be necessary to increase the likelihood of detecting significant results. Locations for ecologically confined testing of GMMs will be selected in part for their isolation. For design of trials for epidemiological efficacy, the influence of seasonal and inter-annual variations and spatial heterogeneity in incidence of infection or disease, as well as the prominence of the targeted mosquito species in disease transmission, must be considered. GMMs are expected to be tested in the context of conventional control measures recognized as the standard of care. Thus, the effect of other ongoing control measures on the outcomes of the GMM trials must be considered in the trial design. The efficiency of GMMs relative to conventional control will in part determine their utility.

Safety evaluation

Assessment of the safety of GMMs will be an ongoing requirement throughout the development pathway. At each phase or logical point in the testing pathway, risk analysis will contribute to determining whether to allow trials to move forward. Risk analysis typically follows a standard multi-stage process that should inform and articulate the concerns on which to focus and the acceptability of risks. Release of GMMs raises different but not entirely novel issues compared to those previously addressed for other genetically modified organisms (GMOs). There is a considerable amount of literature and examples available to guide the risk analysis of GMMs and GDMMs.

The concept of risk takes into account both the likelihood and the magnitude of harm that may occur from a specific action, particularly with regard to national protection goals. Risk assessment is a methodological approach to systematically define the level of risk. Risk assessment should be conducted on a case-by-case basis, taking into account the characteristics of the GMMs, the receiving environment, and the conditions of use. Thus, risk assessment should be proportionate to the particular phase of testing. Risk assessment should consider: potential sources of harm stemming from the planned action (hazards); the magnitude of each harm if it were to arise; potential routes and anticipated level of exposure to these harms; estimated likelihood of the harms occurring; and levels of uncertainty associated with this estimation.

The identification of hazards does not in itself indicate an unacceptable risk. Upon evaluation, risk in some cases may be judged as acceptable, for example, when the probability of a harmful event occurring is determined to be very low and/or the consequences of it occurring would be negligible. Risk management will evaluate proportionate measures that are needed to mitigate any harm or reduce uncertainty, and develop both standard and responsive measures to make any identified risks acceptable to communities and regulators. Risk communication involves an ongoing and iterative exchange of information and opinions concerning risks and risk perceptions that will contribute to planning for risk assessment and risk management, and will be part of community engagement activities.

Independent ongoing safety review during GMM testing is recommended, covering relevant aspects of health and environmental monitoring. This may be accomplished through existing institutional or national-level biosafety committees and/or establishment of project-specific review bodies. Strengthening of biosafety oversight capabilities within disease-endemic countries as necessary should be encouraged as a priority.

The risk of novel technologies such as GMMs may be considered in the context of relevant alternatives, such as the risk of no action or the risk of conventional control methods. “Causes more harm” than current practice has been proposed as a reasonable benchmark for decision-making on GMM-based vector control systems. For GDMMs, a safety criterion for moving to field testing has been articulated as a well-reasoned justification that they will do no more harm to human health than wild type mosquitoes of the same genetic background and no more harm to the ecosystem than other conventional vector control interventions.

The evaluation of risk should be set against the benefits of GMMs for improving human health on a case-by-case basis. Impact assessment considers the potential adverse, neutral or beneficial changes that may result from testing or implementation of GMMs, including health, socioeconomic

and ecological impacts. If and when a decision is made to implement GMMs broadly as a public health tool, there will be a need for post-implementation quality control and surveillance to monitor for ongoing effectiveness and safety, according to any specific risks identified by pre-implementation risk assessment.

Ethical considerations

In the design and conduct of GMM trials, a key set of questions is related to the ethical implications, including the nature and scope of the obligation to host communities and what type of protections should be provided to them. Respect for communities should be understood as an overarching ethical goal within trials of GMM technologies. Although activities of ethical reflection and engagement often overlap with those of regulatory compliance, ethical issues and responsibilities are generally broader than just those activities specifically mandated by administrative law or organizational policies. It should not be assumed that regulatory compliance implies that ethical responsibilities have been adequately addressed.

Democratic governance of new technology requires that proposals such as field testing of GMMs be discussed and debated. Developers must communicate the aims and methods of the research, as well as the potential risks and benefits in a transparent and accessible manner. Discussion should be conducted in a way that receives the attention of scientists and decision-makers and ensures that stakeholders' voices are heard.

Ethical obligations to different stakeholder populations will vary and may be addressed through a range of activities.

- Interactions with individuals that involve collection of clinical specimens or that give rise to individual or household-level identifiable data will, in the absence of specific exceptions or waivers, require informed consent.
- For those individuals living in or near a trial site who are not, as traditionally defined, subjects of the research at hand, but who nonetheless may be affected by the conduct of research, community engagement and authorization practices address the ethical obligations to respect their interests, respond to their collective concerns, and reach agreement about whether the research should proceed.
- With publics not immediately associated with the trial site but who take an interest in the conduct or outcome of the research, the ethical obligation is not to proactively seek them out but to consider and respond to their expressed concerns and interests in a respectful manner. GMM projects should incorporate a communications/public engagement strategy that not only includes information about the goal and methods, but also provides opportunities for follow-on discussion.

A co-development approach, which recognizes the importance of knowledge engagement with scientists and publics in countries where the product will be tested or implemented, is fundamental to all facets of research on GMMs. Research must be conducted in a manner that promotes and fosters leadership by in-country scientists. Communities must be given the opportunity to interact with the research team and to shape the process of engagement and authorization of field research.

Engagement will be an iterative process that continues throughout the development pathway. Ethics and engagement activities must be considered before Phase 1 proof-of-concept work has been completed. Community engagement activities should begin before the collection of baseline field data. Plans at this stage should also include initiating discussions with policy-makers to explain research goals and develop an open dialogue.

Before proceeding to field testing, plans should be developed for responding to ethical obligations to individuals or households being asked to participate, as well as communities being asked to host these studies. Communications should explain that these are research activities intended to test the efficacy of a new technology. Since a protective effect is not assured, the community must continue to employ other available methods to protect themselves from disease transmission. Community engagement and authorization activities will expand in Phase 3, and human subject issues will become more prominent in trials undertaken to determine the epidemiological impact of GMMs. In Phase 4, ethical responsibilities to those who are affected by the technology are increasingly likely to converge with established processes. Implementation of GMMs will be a public health initiative taking place in the context of existing legal, regulatory and political institutions. However, the need for public engagement activities is likely to continue.

It will be important for members of the scientific team to be involved in ethics and engagement activities. However, many aspects of these activities will also require the specialized skills of social scientists and communications experts. Adequate funding for these activities will be imperative for the successful accomplishment of the research objectives. A need can be anticipated for training project scientists in research ethics, and for training institutional or national ethics review committees in the specialized issues associated with vector biology research.

Regulatory frameworks

Regulation is an enabling process that ensures that safety and efficacy are consistent with social values. Regulation of GMMs will be encountered early in the research process and throughout development and implementation. Many aspects of legislation may be pertinent to the regulation of GMMs. Regulation can be expected at institutional, state, provincial and national levels, all of which may have to be addressed concurrently. International treaties and conventions may also be relevant. Other recommendations and policies issued by authorized agencies and regional and international bodies may provide important context and guidance.

Each country has its own sovereign regulatory process. Regulation of GMMs as public health tools could involve multiple regulatory authorities. Early investigation of the regulatory processes in the potential partner country and open communication with the national officials, risk assessors and decision-makers is imperative in order to understand the requirements relevant to GMMs. Early and proactive communications with regulatory agencies will also help to build understanding about the goals and methodologies of the project. There may be a need to strengthen familiarity with entomological research methods and/or biosafety procedures, and this should be planned for accordingly.

The Cartagena Protocol on Biosafety is accepted by almost all developing countries and is anticipated to have an important influence on GMM regulatory processes and risk assessments. It will be essential to work with regulators to ensure understanding of the differences between

GMMs and GM plants or crops, including the fact that human health benefits are relevant as part of the regulatory decision-making process for GMMs. National biosafety laws and regulations developed primarily to regulate GM plants may need to be reinterpreted for GMMs, or additional guidance provided. Consequently, the regulation of GMMs may present potential delays and unanticipated costs that must be recognized as early as possible. Plans for dealing with such contingencies should be put in place and suitably resourced.

Informed public involvement in the regulatory decision process for GMMs is a necessity if implementation is to gain public acceptability. Regulatory processes often include formal public consultation opportunities, in addition to opportunities for participation in project-led engagement activities.

While there is currently no standardized procedure beyond the Cartagena Protocol for addressing the potential transboundary movement of GMMs or GDMMs, precedents exist for regional cooperation in the areas of health and agriculture. A regional notification and agreement process is advisable for planned introductions capable of autonomous international movement.

1. Introduction

SUMMARY

The need for additional methods to combat mosquito-borne diseases is widely recognized. Recent research offers the possibility that genetically modified mosquitoes (GMMs) could be used as complementary tools to prevent pathogen transmission. GMMs provide several theoretical advantages that make them attractive for vector control, such as their specificity and ability to function in areas that are difficult to reach with conventional control methods. Different GMM technologies under consideration include those aimed at reducing the number of mosquito vectors in a given region (population suppression) or rendering the local mosquitoes less able to transmit a pathogen (population replacement). Both types of technology can be designed so that the modification is limited in its persistence (self-limiting) or spread (localizing) in the environment, or so that the modification is passed on through interbreeding populations of wild mosquitoes of the target species (non-localizing) and persists indefinitely within the local mosquito population (self-sustaining).

Different GMM approaches may be best suited for different needs. Self-limiting and localizing approaches may be attractive from an environmental safety perspective, as environmental exposure is expected to be more restricted. These approaches, however, will require more releases to maintain long-lasting and widespread effectiveness against target diseases. Self-sustaining and non-localizing approaches could ultimately provide more durable and cost-effective public health solutions, but are unlikely to remain within national borders.

A testing pathway in which new GMM strategies move from the laboratory to small-scale testing in more natural environments and finally to larger open release trials is recommended, with each transition dependent upon satisfactory demonstration of efficacy and safety. When GMMs are incorporated into national or regional vector control programmes, the need for ongoing monitoring of effectiveness and safety should be considered in order to ensure acceptable quality and performance standards and inform any necessary management responses.

Current mosquito control efforts rely heavily on methods such as insecticide-treated bed nets (ITNs), indoor residual spraying (IRS) with insecticides, outdoor insecticide fogging, application of chemical larvicides, and management of standing water to reduce mosquito larval breeding sites. Despite diligent application of the available control strategies, including improvements in and expanded use of bed nets, mosquito-borne diseases such as dengue and malaria continue to pose major global health challenges *(1)*. Malaria control efforts have stalled in high-incidence regions *(2)*, and experts have stated that eradication will not be achieved with current tools alone *(3)*. This has prompted renewed calls for investment in the research and development of new vector control tools *(4, 5)*. Similarly, dengue incidence continues to increase *(6, 7)*, imposing a substantial public health and economic toll *(8–10)*. WHO has acknowledged that innovative vector control tools are also badly needed for dengue control and prevention *(11)*. Outbreaks of other arbovirus infections also underscore the need for better mosquito control methods *(12, 13)*.

Limitations of current vector control methods include: difficulty reaching mosquito larval breeding sites and adult resting sites; evolution of resistance to insecticides; compliance and infrastructure issues; concern about the impact of insecticides on the environment and/or toxicity to humans; and, importantly, cost. The ongoing costs of vector control are substantial *(14, 15)*, and maintaining the high levels of donor and national government support necessary to achieve high coverage of control measures over long periods of time has historically proven daunting *(16–18)*. Therefore, for both operational and economic reasons, there is a recognized need to add new, sustainable and cost-effective vector control tools.

In the late 1980s, intense interest arose in the application of modern genetic engineering technology to arthropod vectors as a potential approach to limit the transmission of human pathogens *(19)*. Subsequent research has focused in large part on two high-impact mosquito species, *Anopheles gambiae* and *Aedes aegypti*, which serve as major vectors for malaria and dengue, respectively.

Key points

- **GMMs show promise as complementary tools for control and elimination of mosquito-borne diseases.**
- **Different modification approaches are under investigation, including those that reduce population size of vector mosquitoes or make them refractory to certain pathogens and those that allow these characteristics to persist and spread in the local population of vector mosquitoes to various extents.**
- **A phased testing pathway is recommended, which starts with contained research in indoor facilities and then moves to small-scale followed by larger scale field releases.**
- **The decision to release GMMs must be preceded by careful evaluation of their safety and efficacy.**
- **Decision making should take both benefits and risks into account; acceptability and deliverability are also important elements of the development pathway.**

Substantial progress has been made on challenges, such as sequencing the genomes of these two important vector species, achieving stable germline transformation, identifying sex-, tissue- and stage-specific DNA control elements, identifying the genes involved in susceptibility or resistance to infection/insecticides, and developing methods to spread heritable modifications to native mosquito populations within an epidemiologically relevant timeframe as needed to achieve disease control. The initial technical objective (germline transformation) has been accomplished in all major mosquito genera and can be considered routine for several species *(20–23)*. Likewise, effector mechanisms have been developed, establishing proof of principle for either refractoriness or sterility, e.g., *(24–28)*. Efforts can be envisioned to develop additional effectors, such as those to reduce life span or alter behaviours (e.g., host-seeking) in a beneficial way. Considerable progress has also been made in identifying molecular designs that can promote the inheritance of effector modifications within interbreeding populations. Most of these designs mimic mechanisms found in nature, such as target site cleavage-based mechanisms, toxin-antidote based mechanisms or engineered translocations *(28–31)*. Technical advances in the research and development of GMMs support the need to explore whether they may supplement or provide alternatives to existing interventions, contributing to the reduction or even prevention of disease transmission *(32)*.

The pathway towards the successful implementation of genetic technologies for the control of mosquito-borne diseases will require a multidisciplinary effort encompassing not only additional scientific advances, but also complementary planning for ethically and environmentally responsible testing, and reliable, cost-effective and socially acceptable implementation. Consequently, a technical consultation on GMMs was organized in May 2009 by the Special Programme for Research and Training in Tropical Diseases of the World Health Organization (WHO-TDR) and the Foundation for the National Institutes of Health (FNIH), which recommended that a guidance framework be developed for assessing the safety and efficacy of GMMs and addressing the regulatory, ethical, social and cultural issues related to the development and testing of GMMs *(33)*. In response, the first *WHO Guidance framework for testing of genetically modified mosquitoes* was published in 2014 *(34)*. The revised framework presented here reflects technical advances and knowledge accrued since that time. Like the earlier version, it is intended to provide a basis for conducting trials according to best practices, which will contribute to the comparability of results and credibility of conclusions. This should facilitate decision-making by countries regarding the potential testing and use of GMMs as public health tools for the prevention and control of malaria, dengue and other mosquito-borne diseases.

1.1 GMM strategies

The currently contemplated GMM technologies are designed to have the following two major types of effect, both of which are predicted to reduce disease transmission. Theoretically, these two strategies could be used in parallel, where replacement would reduce the vectorial capacity of the mosquito populations that have been reduced in size but not eliminated by suppression mechanisms.

> **Population suppression** (also termed population reduction) – *strategies that target vector density with the intent to reduce (suppress) the size of the mosquito population.* As a disease control tool, the intent is to reduce the population of vector mosquitoes to the extent that it would not be able to sustain pathogen transmission. These approaches include methods to reduce the overall numbers of female mosquitoes (with or without a concomitant direct effect

on males), which would result in decreased reproduction and a decline in the population. Examples of how this could be accomplished include biasing against the development of female progeny (sex-ratio distortion), reducing female fertility, or shortening the lifespan of female mosquitoes, thereby decreasing the length of time available to reproduce and transmit a pathogen from one person to the next.

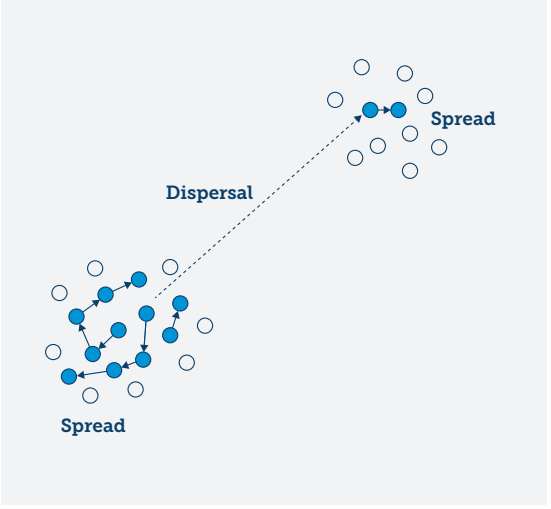
Population replacement (also termed population modification, alteration or conversion) – *strategies that target mosquito characteristics or functions required for pathogen transmission.* This involves the introduction of engineered DNA and/or the manipulation of endogenous mosquito genes in a way that would inhibit parasite or virus replication and thus reduce vector competence. In the context of a gene drive system (Section 1.2), upon release into the environment, these GMMs would introduce the change into the local mosquito population through mating, "replacing" the mosquitoes' inherent ability to spread the targeted pathogen with a reduced or eliminated transmission capability.

1.2 GMM approaches

GMM strategies can be further categorized according to their performance characteristics. These include the ability of the transgenic construct to persist in the environment following release (Table 1.1) and/or to spread to interbreeding populations of the target mosquito species via mating *(35)*. These characteristics will depend largely on a combination of two features. The first is the "fitness cost" associated with the modification (a decrease in the mosquito's ability to survive and reproduce as a result of the genetic modification), and the second is transmission advantage, or "drive" (a phenomenon of biased inheritance in which the ability of a genetic element to pass from parent to offspring is enhanced, leading to the preferential increase of a specific genotype from one generation to the next) *(36)*. The complete set of genetic elements comprising the modification intended to confer a desired phenotype (the transgenic construct) in the mosquito form a GMM system.

In this context, spread refers to the transmission of the GMM system to other individuals within an interbreeding population through mating and inheritance; it is distinct from dispersal, which refers to the movement of individuals to a different habitat (Fig. 1.1). GMM coverage of an area will depend on both the spreading characteristics of the GMM system and the dispersal characteristics of the vector. For example, *Aedes* typically do not move long distances, whereas *Anopheles* have been observed to disperse more widely. Moreover, mosquito population dynamics, such as seasonal fluctuations in mosquito numbers or migration exchange with

Figure 1.1 Spread vs. dispersal



neighbouring populations *(37)*, can influence the performance of GMMs in the field. In some cases, systems using similar molecular mechanisms may demonstrate different levels of persistence and spread depending on their exact configuration, which, for example, can result in differences in when, where, or the extent to which the transgenes are expressed. Prediction of GMMs' behaviour, therefore, should take all of these factors into account.

Drive, or gene drive, refers to a phenomenon observed in sexually reproducing organisms, whereby a particular gene is able to bias inheritance in its favour so that the gene becomes more prevalent in the population over successive generations *(36)*. Gene drive elements, such as transposons, sex distorters, toxin-antidote systems, and homing endonucleases, are widely prevalent in nature *(38)*. Progress in molecular biology research has revealed methods to create synthetic gene drives, most of which mimic naturally occurring mechanisms. Gene drive-modified mosquito (GDMM) systems currently under investigation generally exhibit drive due to either over-replication mechanisms (in which the transgenic construct replicates more often than other genes) or interference mechanisms (in which the transgenic construct interferes with the inheritance or function of wild type genes).

1.2.1 Classification by temporal characteristics

The combined effect of fitness cost, which works against persistence of the transgenic construct, and drive, which promotes its persistence, will dictate how long the GMMs remain effective in the field and thus how often additional GMM releases will be required to maintain a reduction in disease transmission.

Self-limiting (also termed self-exhausting) – *approaches in which the modification is expected to be temporally limited and effectively disappear from the target population in the absence of periodic releases of additional GMMs.* Self-limiting approaches are designed to impose a significant fitness cost. In general, the greater the fitness penalty, the shorter the time period over which the GMMs would be expected to maintain their effectiveness. In some cases, the genetic modification may aim for sterility (i.e., the GMMs do not reproduce) or late-acting lethality (i.e., the GMMs reproduce, but most of their progeny do not survive to adulthood). Other self-limiting approaches might impose a less severe fitness cost or incorporate a transient (temporally limited) form of drive. In this case, the modification is expected to disappear more gradually when releases stop, but eventually be lost from the target mosquito population. The number of generations over which the modification will remain apparent will vary according to the GMM system employed. Because self-limiting approaches will require ongoing releases to maintain effectiveness, the effects of self-limiting GMMs are expected to be reversible by discontinuing releases. Some have suggested that the release of mosquitoes containing self-limiting constructs should be considered prior to field testing of mosquitoes with self-sustaining constructs in order to gain experience with environmental interactions, but under circumstances where effects could be reversed by halting releases *(39, 40)*.

Self-sustaining (also termed self-propagating or self-perpetuating) – *approaches in which heritable modifications are intended to become stably established within interbreeding target mosquito populations.* Self-sustaining approaches intend to spread the transgenic construct through native mosquito populations within an epidemiologically relevant timeframe. This requires a strong drive mechanism capable of overcoming any fitness costs associated with the modification and rapidly increasing the frequency of the transgenic construct from low initial levels to fixation (or near fixation). Once established, self-sustaining approaches are intended to be relatively stable and to require only smaller and infrequent secondary releases at most to maintain effectiveness. Suppression strategies could lead to elimination of a local population. However, persistence of the effect may be influenced by local conditions, such as extended dry periods that severely reduce the modified mosquito population, or by the accumulation of resistant mutations that prevent the construct from spreading or exerting its desired effect.

Table 1.1. GMM strategies classified by temporal characteristics

Strategy	Approach	
	Self-limiting	**Self-sustaining**
Population suppression	- Modification reduces the number of mosquitoes available to transmit pathogens - Will not pass the modification to progeny or will pass on the modification through interbreeding populations only for a limited number of generations - Modification not intended to persist in the absence of continued releases	- Modification reduces the number of mosquitoes available to transmit pathogens - Will pass the modification through interbreeding populations indefinitely in the absence of resistance developing - Modification intended to become fixed and to persist indefinitely or until the local mosquito population is eliminated
Population replacement	- Modification interferes with a function important for pathogen transmission - Will pass the modification through interbreeding populations for a limited number of generations - Modification not intended to persist in the absence of continued releases	- Modification interferes with a function important for pathogen transmission x - Will pass the modification through interbreeding populations indefinitely in the absence of resistance developing - Modification intended to become fixed and to persist within the population

1.2.2 Classification by spatial characteristics

Localization characteristics will be directly related to propensity for spread and dispersal (Table 1.2). Spread will be related to persistence characteristics. Drives intended to be transient are less likely to spread the modification widely within the local population of target mosquitoes than drives intended to be self-sustaining. Spread of the modification into neighbouring mosquito populations will be a property of both the movement pattern of the mosquitoes and the drive "threshold". The term threshold refers to the proportion of GMMs, with respect to the total population of the target mosquito species, above which a drive system will be maintained and

possibly increase in frequency, but below which it is predicted to decrease in frequency. High-threshold drives *(41)* are designed so that the GMMs must be present at high frequency to establish and spread the transgenic construct within the target population. This necessitates relatively large initial releases of GMMs. Threshold-independent or low-threshold drives can initiate establishment of the transgenic construct within populations of the target mosquito species following a rare introduction or low initial release frequency, respectively. The lower the threshold, the more likely it is that the dispersal of low numbers of GMMs would be sufficient to initiate spread of the modification to other areas where interbreeding mosquito species containing the target of the drive mechanism are present.

Localizing – approaches in which the distribution of the modification is intended to be spatially restricted. These approaches are not intended to spread the modification substantially beyond the target area or population. GMMs with modifications leading to sterility or with non-driving modifications are expected to remain geographically confined after release. Self-limiting and high-threshold drives are likely to demonstrate restricted spread and dispersal. Other localizing mechanisms are also possible, such as those that can limit the effect of certain gene drive systems to a local subpopulation of the target species based on geographically restricted, or "private", genetic polymorphisms *(42)*.

Non-localizing – approaches in which the modification is intended to distribute widely within interbreeding populations. Self-sustaining drives are more likely to be non-localizing because the longer a drive is effective, the more likely it is that it will spread widely within the local population of target mosquitoes. A self-limiting drive that persists through many generations could also spread the modification substantially throughout the local population. The potential for dispersal to connected interbreeding populations will be influenced by drive threshold, as well as by mosquito migration characteristics and ecological factors.

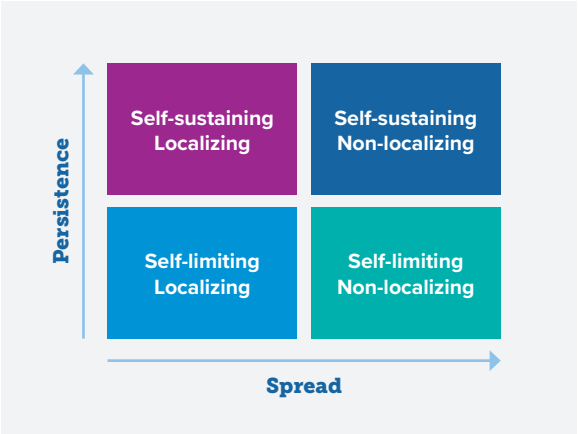
Table 1.2. GMM strategies classified by spatial characteristics

Strategy	Approach	
	Localizing	Non-localizing
Population suppression	- Modification reduces the number of mosquitoes available to transmit pathogens - Modification not intended to distribute the modification far beyond the initial population into which it is released	- Modification reduces the number of mosquitoes available to transmit pathogens - Modification intended to distribute through interbreeding populations containing the target of the drive, possibly including those that are remotely connected
Population replacement	- Modification interferes with a function important for pathogen transmission - Modification not intended to distribute far beyond the initial population into which it is released	- Modification interferes with a function important for pathogen transmission - Modification intended to distribute through interbreeding populations containing the target of the drive, possibly including those that are remotely connected

1.2.3 Example GMM systems

Examples are briefly provided here to illustrate the breadth of possible GMM systems (Fig. 1.2); however, these do not represent a comprehensive list of all current and envisioned technologies. More complete descriptions are available elsewhere, e.g., *(29–31, 35, 36, 43–53)*. Several GMM systems currently under investigation for the control of mosquito-borne diseases are still theoretical or have only achieved proof of principle in other insect species. It is expected that additional GMM systems will continue to be explored as this area of research progresses.

Fig. 1.2. Possible GMM categories



In considering these examples, it must be emphasized that, for some systems, there may be a spectrum of spread and persistence characteristics, depending on their specific design and the context in which they will be used (or assumptions used in modelling). Since ecological conditions can affect the fitness of the GMMs, and thus affect both persistence and threshold, this is an important consideration for predicting localization *(55)*.

Self-limiting, localizing modifications – GMM approaches employing transgenic constructs that do not drive will require frequent inundative releases to maintain effectiveness, and any effect on disease reduction will be limited to areas where releases are ongoing. Temporally limited gene drive systems are expected to require less frequent and smaller releases.

- *Genetic sterility techniques* are intended to function similarly to the classic radiation-based sterile insect technique (SIT) that has been used successfully against pest insects affecting livestock and crops *(39, 56, 57)*. In this case, few, if any, viable offspring are expected to result from the mating of GMMs with native mosquitoes in the target population. The reproductive potential of the local population, therefore, is expected to decrease, resulting in population suppression. A version involving release of GMMs carrying a dominant lethal gene *(58)* has been field tested and found to reduce mosquito density while releases are ongoing *(59, 60)*. Another version termed precision-guided SIT, which disrupts genes important for female viability or male fertility, has been proposed for mosquitoes and agricultural pests *(61)*.
- *Female-specific lethality* is a non-driving population suppression system in which male GMMs are homozygous for a repressible dominant transgene that is disabling or lethal for females at some stage of their development *(62, 63)*. When the fertile modified males are released and mate with local female mosquitoes, their female progeny do not survive. Heterozygous male progeny are viable, however; these pass the transgenic construct

to their offspring, resulting in only male progeny. Because there is no drive mechanism, the modification will be passed on according to Mendelian inheritance, becoming less prevalent within the population over successive generations of crossing with native mosquitoes. The fitness cost associated with the modification will accelerate its loss from the population.

- Autosomal endonuclease-based *male bias* is another non-driving population suppression system that impacts populations similarly to the female-specific lethality system. In this case, a transgenic construct located on an autosome produces a DNA endonuclease that specifically disables the female sex chromosome. This causes most sperm to carry the male sex chromosome, resulting in a decreased proportion of female offspring. Decreasing the number of female mosquitoes in the population reduces reproductive potential *(64, 65)*. As is the case with female-specific lethality, the modification will be passed on by male offspring according to Mendelian inheritance and fitness cost.
- *Split drives or Daisy drives* consist of two or more unlinked transgenic elements in which each exhibits drive only in the presence of a companion element *(51, 66)*. When configured appropriately, these gene drive systems are predicted to persist for a limited time, after which they decay due to dissociation of the elements. Limited persistence of the complete system is expected to result in spatial restriction. These drives have primarily been proposed for population replacement.

Self-limiting, non-localizing drive modifications – GMMs in this category would contain a transient drive mechanism that could persist long enough to spread the modification beyond the target release area or mosquito population. It is debatable whether any current GMM strategies conform to this category, as the classification depends on the scale of localization that is of interest. For example, the extent to which Daisy drives are localized is predicted to depend on the number of elements in the chain *(66)*, potential for migration exchange with neighbouring populations of the target species (dispersal), and fitness cost associated with the transgenic construct *(37)*.

Self-sustaining, localizing drive modifications – Various GMM systems have been proposed that are intended to persist locally but have limited ability to spread the transgenic construct beyond the local mosquito population into which it is initially introduced. The scale and frequency of releases required to maintain effectiveness, as well as the range of spatial spread, are likely to be highly dependent upon the system and the use context *(41)*.

- *In underdominance (UD)-based systems,* hybrids between two true-breeding strains (e.g., gene drive strain and wild type) have lower fitness than either of the true-breeding parental strains *(47, 67, 68)*. Releases of UD gene drive homozygotes above a threshold frequency are expected to drive the population towards homozygosity for the transgenic construct. This threshold depends on the relative fitness of the gene drive-modified and wild type mosquitoes, but is likely to be 25% or higher; consequently, this is a high-threshold drive system. UD systems have mainly been proposed to carry transgenes into local mosquito populations for population replacement approaches.

Self-sustaining, non-localizing drive modifications – Several systems have been proposed that will promote prolonged persistence and spread of the transgenic construct in interbreeding populations. These are low-threshold or threshold-independent drives. Computer simulations support the potential for self-sustaining approaches to eliminate disease in some circumstances *(69, 70)*. Examples include the following:

- *"Maternal effect dominant embryonic arrest (Medea)"* involves a combination of a maternally expressed toxin and a zygotically expressed antidote. This is a hybrid incompatibility system in which offspring that do not inherit the transgenic antidote construct do not survive, while those that do inherit the antidote survive at different rates depending on whether it came from their father or mother *(44, 71)*. Engineered Medea systems have been shown to demonstrate strong drive in other insects *(71, 72)*, and theoretically could be used for population replacement in mosquitoes (73).
- *"Y-linked male bias"* is a strong sex-ratio distortion system similar to the autosomal endonuclease-induced male bias system in *Anopheles*, except that the female (X) chromosome-disabling DNA endonuclease construct is situated on the male (Y) chromosome and thus will be inherited at high frequency. Males with the Y-linked transgenic construct produce only male progeny, thereby reducing the numbers of female mosquitoes over multiple successive generations in a population suppression strategy *(69)*.
- *"Homing drives"* may utilize naturally occurring homing endonuclease genes or synthetic constructs coding for a DNA endonuclease gene targeted to a specific DNA sequence. In heterozygotes, the transgenic construct received from a GDMM parent is located at a precise genomic location and produces an endonuclease designed to cut the exact same location on the homologous wild type chromosome. Natural double-strand DNA repair processes result in the transgenic construct being copied into the repaired chromosome, in some cases with very high efficiency. This efficient conversion of target cells, e.g., germline cells, from heterozygotes into homozygotes creates strong drive, with preferential inheritance of the transgenic construct repeating in subsequent generations, resulting in high persistence and spread. Homing drives can be used for population suppression when they target genes involved in the fitness or fertility of female mosquitoes *(27, 63)* or for population replacement if the transgenic construct codes for an anti-pathogen or other effector *(74)*.

Research is also ongoing to develop *control systems* capable of neutralizing self-sustaining gene drive systems in response to concerns about their reversibility in the event of unintended consequences. Methods to overwrite, reverse or block gene drive have been proposed *(75)*. Certain genetic systems for either inactivating or eliminating homing drives have been successfully tested in *Drosophila* in the laboratory *(76, 77)*, and additional self-elimination methods have been suggested *(78)*. In addition to genetic mechanisms, chemical systems in which the inheritance probability of the gene drive can be controlled by a synthetic, orally available small molecule have been demonstrated in *Drosophila (79, 80)*. If such systems are found to be applicable to mosquitoes, it will be important to evaluate their potential by modelling realistic use conditions *(81)*.

1.3 Characteristics of GMMs

GMM technologies offer certain potentially favourable design characteristics as new vector control tools.

- They could provide area-wide protection that is accessible to everyone, regardless of their socioeconomic level or proximity to medical facilities.
- They would not impose an additional burden by requiring people to change their behaviour in order for the intervention to be effective.
- They would not require application of a chemical that must come into direct physical contact with the mosquito to be effective.
- They could reach mosquito populations and their larval breeding sites that have been traditionally the hardest and most expensive to reach using conventional vector control strategies, by exploiting the mosquitoes' natural seeking behaviour to find mates and oviposition sites. This would include outdoor and/or day-biting vectors that escape control by ITNs and IRS, but that may play an important role in transmission.
- They are capable of a high level of specificity and stability that would reduce the ecological, environmental and human health hazards associated with broad-spectrum insecticides.
- They can be developed to suit the requirements of both urban and rural environments.
- Technologies aimed at population suppression could reduce transmission of all pathogens transmitted by the same vector mosquito. For example, suppression of *Aedes aegypti* vectors could reduce transmission of multiple arboviral diseases.

Self-sustaining approaches have additional predicted characteristics that would be useful in disease elimination or eradication efforts.

- Limited need for reapplication would minimize the requirement for ongoing mass production and delivery, which should make their use relatively inexpensive.
- Durability of activity should maintain its effectiveness, even in situations where other disease control methods must be temporarily suspended, for example, due to adverse weather conditions, civil unrest, or outbreaks of unrelated diseases *(82)*.
- Population replacement technologies would reduce or eliminate the pathogen, rather than a particular mosquito vector, thereby alleviating concerns that producing an empty ecological niche would allow other competent vectors to invade the treated area.
- Some of the technologies could affect more than one local vector species if cross-mating occurs even at low levels, thus having the potential to reduce a disease in regions where it is transmitted by related species.

The theoretical disadvantages and risks of genetically modified, and especially gene drive-modified, organisms also have been widely described, e.g., *(83–91)*. For example:

- Some have voiced concerns over the possibilities that GMMs, especially GDMMs with self-sustaining, non-localizing drive systems, could cause harm to human or animal health, biodiversity, or water quality *(40, 92, 93)*.

- Concerns have also been raised about the stability and predictability of GDMMs' effect, including the potential for off-target or non-target effects.
- Currently, there are limited possibilities for control, mitigation or remediation if adverse effects from self-sustaining drives are encountered.
- Other potential issues are the development of resistance over time on the part of either the mosquito or the pathogen (Section 2), and the loss of immunity to the relevant pathogen(s) by people in treated areas over time. With regard to the potential health impact, these possibilities also apply to other commonly used control methods such as insecticides and drugs.

Research is underway to address these concerns, all of which must be considered in risk assessment (RA) and risk management (RM) planning (Section 3). It is necessary to consider these on a case-specific basis in the context of the particular modification in question, the characteristics of the organism that is being modified, and the intended use of the modified organism. Only on such a specific basis can risks be appropriately assessed and RM options contemplated.

The choice of GMM approach will be influenced by considerations of benefit and risk under the foreseen use scenarios. This will be a fundamental determination in formulating the target product profile for a GMM intervention (Section 2). For example, an early and ongoing goal of GDMMs has been to provide a low-cost, durable and highly efficacious tool for disease control that is adaptable to varied disease transmission conditions. Such an efficacy goal, however, has been countered by concerns over safety uncertainties. GMMs with limited potential for spread and persistence will by design offer less durable protection over smaller areas and with greater requirements for production and delivery; however, such GMMs may elicit fewer safety concerns. Decisions on the desirable safety and efficacy characteristics of a GMM product are best made in consultation with affected communities (Section 4). Researchers are advised to consult relevant potential end users, both government authorities and communities, to understand market needs early in the development process. Questions about the appropriate regulation and governance of GMMs have been raised, e.g., *(84, 94–96)*, and both the need for and extent of public consultation should be an important consideration in the development of GMMs (Sections 4 and 5).

1.4 Potential utility of GMMs

GMMs are primarily being developed for use within disease-endemic or epidemic situations as part of an area-wide control programme to reduce the rate of pathogen transmission. GMM characteristics may influence the choice of an integrated approach to achieve a particular entomological and/or epidemiological efficacy goal.

GMMs are likely to be used in conjunction with other disease control methods. GMMs are compatible with the use of drugs and vaccines, as well as common vector control methods such as source reduction. Assuming the local mosquito population is not more insecticide-resistant, GMMs can also be compatible with insecticide-based control methods. GMM-mediated methods to reduce the force of disease transmission by reducing the number of infectious bites could improve the protective potential of other control tools. For example, modelling suggests that a pre-erythrocytic malaria vaccine would be much more effective in low-transmission settings than in high-transmission settings *(97, 98)*. Conversely, concurrent use of a vaccine would reduce the possibility that prolonged reduction in pathogen exposure due to effective transmission control by

GMMs might result in loss of immunity within the human population *(99)*. Moreover, use of GMMs could contribute to the reduction of insecticide use and consequently reduce selection pressure on vector populations for development of insecticide resistance.

GMMs could provide a valuable tool for disease eradication. Because they would not require a high level of individual participation, GMMs may not be as susceptible to the lack of compliance that is sometimes seen with conventional control measures after disease rates fall and the perceived disease threat is low. Ongoing area-wide protection provided by GMMs, especially through self-sustaining approaches, could prevent the reintroduction of the pathogen into the population (for example, by immigration of infected persons or mosquitoes) after successful regional elimination efforts.

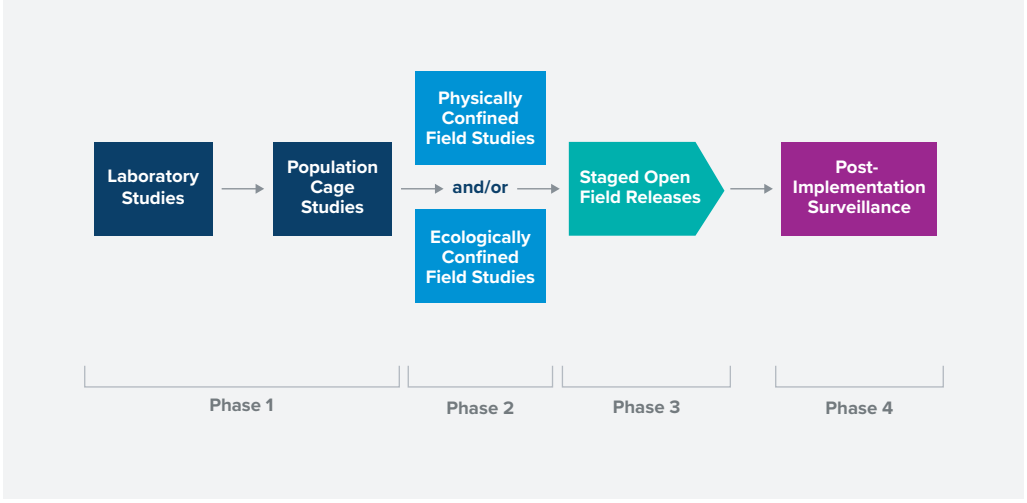
Certain GMM technologies could also be useful as a preventive measure in regions where disease is not yet occurring. For example, where exotic mosquito species may be introduced, GMMs could help to prevent their establishment. This is analogous to the current utilization of SIT to prevent Mediterranean fruit fly infestations in otherwise pest-free areas.

1.5 GMM testing pathways

Following initial progress in developing genetic transformation methods for a range of mosquito vectors, a series of workshops held in London and Atlanta in 2001 *(100)*, Wageningen in 2002 *(101)*, and Nairobi in 2004 *(102)* initiated a process to discuss the requirements related to the testing and implementation of genetically modified vectors. The concept of phased testing was widely advocated. The recommendation to develop a phased testing pathway was reiterated at a technical consultation held in Geneva in May 2009, which focused on the practical and technical issues associated with moving new GMM technologies from the laboratory to field testing *(33)*.

In accordance with these earlier recommendations, a stepwise testing process is generally recommended for most types of GMMs, as illustrated in Fig. 1.3.

Fig. 1.3. Phased testing pathway for GMMs



For simplicity, Fig. 1.3 describes a unidirectional pathway. In practice, however, repetitions of some segment(s) of the pathway may be required in order to improve the technology and refine the procedures until the requirements for moving to the next phase are met.

Phase 1 is anticipated to begin with small-scale laboratory studies for efficacy and safety testing, followed by testing in larger population cages in an indoor setting, conducted under appropriate containment facilities and procedures, e.g., *(103, 104)*. Laboratory testing under highly controlled conditions will enable preliminary assessment of whether the GMMs demonstrate the desired biological and functional characteristics, with an eye on future efficacy and safety.

For those GMMs showing promise in Phase 1, **Phase 2** will initiate confined testing in a more natural setting that will enable some observation of interaction with the native mosquito population and other elements of the ecosystem, but under conditions that will limit release into the environment. Small trials in Phase 2 may involve testing under physical confinement (often termed containment) within a large cage that simulates the disease-endemic setting, while minimizing the possibility of escape. This approach is sometimes called semi-field testing. Phase 2 testing may also involve small-scale ecologically confined field release. Ecological confinement entails geographical/spatial and/or climatic isolation intended to limit the outward migration of GMMs into the environment. The decision on the requirements for one or both components of Phase 2 testing will be made by national regulatory authorities and will probably depend on the nature of the GMM technology, prior knowledge of its effects in other environments and other factors that are taken into account in the RA process (Section 3).

A situation could arise in which a physically confined trial might not be deemed necessary, for example, when a technology has already been tested and found to be safe in another venue. It should be noted, however, that the regulatory requirements for physically vs. ecologically confined trials are expected to differ, since an ecologically confined trial involves intentional, though limited, release into the environment.

Phase 2 trials will continue the assessment of the biological and functional activity of GMMs, including their effect on local/wild type mosquitoes; however, because of their limited scale, these trials will only rarely provide information on the disease impact of the technology. Moving forward to initiate larger GMM trials in the environment and in disease-endemic countries will require thoughtful consideration and the application of relevant ethical and regulatory practices (Sections 4 and 5). It is recommended that issues of data portability be considered from the initiation of field testing in order to facilitate the broadest possible applicability of results. As data systems are being designed for field trials, existing standards for data collection should be applied.

Contingent upon satisfactory results of confined testing in Phase 2, the GMM technology may proceed to staged open release trials under **Phase 3**. It is likely that this will involve a series of sequential trials of increasing size, duration and complexity, to be conducted at a single site or multiple sites. These trials may be designed to assess performance under various conditions, such as different levels of pathogen transmission, seasonal variations in mosquito density, or presence of other disease vectors in the region. While measurement of entomological parameters is likely to remain the focus of early Phase 3 trials, later trials in this phase may include measurement of the impact of GMMs on infection and/or disease in human populations. Trials to show epidemiological impact must be designed accordingly, with considerable thought on the needs for achieving a

statistically meaningful result. Although still focused on intense examination of the function and efficacy of GMMs, Phase 3 trials effectively institute a limited deployment of the technology.

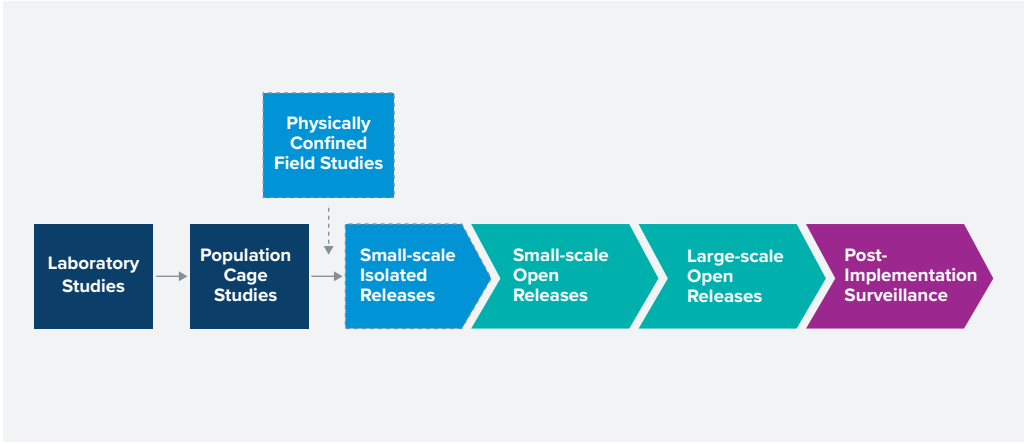
Approval for moving forward to each consecutive phase of testing (Phases 1–3) will be the responsibility of the relevant national authority. The identity of this authority may differ among individual countries, as national legislation or policy may allocate this responsibility to a lead ministry or a board/commission representing several ministries. Several levels of oversight and review will most likely be required before bringing the decision to the national level (Section 5). Therefore, the institution conducting the research will be expected to have its own independent committees overseeing biosafety and the involvement of human subjects. Intermediate jurisdictional units of government may impose additional levels of regulation.

The results of Phase 3 testing will form the basis for determining whether the technology should move into wider scale and more systematic application as part of a national or regional programme for vector and disease control. The ultimate decision on the deployment of GMMs as a public health tool **(Phase 4)** will involve the national regulatory authority, and may also involve authorities responsible for determining national or regional disease control priorities (if different from the regulatory body). Countries may look to WHO for guidance on the utility of GMMs as public health tools *(105)*. Phase 4 constitutes an ongoing surveillance phase that will assess effectiveness under operational conditions (both entomological and epidemiological impact), accompanied by monitoring of safety over time and under diverse situations. Long-term surveillance of safety for human health will be analogous to the pharmacovigilance *(106)* applied in medicine; however, in the case of GMMs, aspects of environmental safety should also be considered. Ongoing monitoring will be aimed at ensuring sustained quality and performance for disease control, and determining whether any changes are needed in the management of either the GMM technology itself or other aspects of an integrated control programme. In this regard, it will be important to ensure that a perceived decrease in the disease threat following implementation of GMMs does not lead people living in the area to become complacent and revert to behaviours that could increase transmission pressure.

1.5.1 Modified testing pathway for GDMMs

The phased testing pathway described in Fig. 1.3 may be applicable to self-limiting or localizing GDMMs depending on their characteristics. However, accelerated progress in the development of self-sustaining, non-localizing (low-threshold) drive systems since 2015 *(30, 31)* has spurred additional thinking on the testing requirements for these systems, recognizing that the characteristics of persistence and spread will have implications for the phased pathway *(40, 84)*. In this case, modelling suggests that the modification could become established in the local population of the targeted mosquito species from the introduction of low numbers of GDMMs *(41, 107, 108)*. Therefore, when Phase 1 (laboratory studies or studies in indoor population cages or environmental chambers) is conducted in a region hospitable to the targeted mosquito species, there is a need for additional precautions in order to avoid escape into the environment, which could lead to premature local establishment of the modification *(109, 110)* (Section 3). Moreover, while there is agreement on the importance of an incremental testing pathway that gradually increases the level of human and environmental exposure to GDMMs subject to fulfilment of efficacy and safety requirements, for

Fig. 1.4 Modified testing pathway for GMMs with low-threshold drive systems[2]



some GDMMs, the characteristics of persistence and spread may make it difficult to delineate distinct cutoffs in Phases 2 through 4 *(40)*. For example, the guarantee of Phase 2 physical confinement becomes uncertain when escape of small numbers of GDMMs could lead to the establishment of the modification in a suitable local mosquito population. Therefore, in regions containing the target species, caution dictates that testing in outdoor cages be considered congruent with the first stage of field release, and appropriate regulatory authorization should be obtained. In addition, trial termination without cause after the initial small-scale field release may be undesirable, since it would prevent observation of longer term effects. Therefore, in the case of self-sustaining, non-localizing GDMMs, field testing may better be conceived of as a continuum of expanding releases (Fig. 1.4).

Here, a biologically relevant precedent can be found in the testing of exotic biocontrol agents that are also expected to spread and persist in the environment after release. Analogous to the testing pathway for such biocontrol agents, there will be a stringent go/no-go safety decision to move from physically confined indoor testing (laboratory or large indoor cage) to field testing (large outdoor cage or initial small-scale release). This decision must take into account an all-hazards RA informed by observations of GDMMs under laboratory and insectary conditions; entomological, ecological and epidemiological data from the proposed field site; and mathematical modelling to predict GMM behaviour at the field site. As in the pathway described in Fig. 1.3, small-scale releases will focus on the assessment of the GDMMs' biological and functional activity, including their effect on native mosquitoes and the local ecosystem. Although absolute ecological containment cannot be guaranteed for mosquitoes modified with a low-threshold drive, initial small-scale release should aim for geographical isolation in order to minimize the possibility of outward migration. As with other types of GMMs, subsequent large-scale testing will include measurement of the impact of GDMMs on infection and/or disease in human populations. Acceptance as a public health tool would initiate scale-up releases and post-implementation surveillance for ongoing safety and efficacy.

[2] Adapted from *(40)*. In this study, large indoor and outdoor population cage studies were considered potentially useful but not on the critical path, as indicated by the dashed lines.

The issues identified for the testing of self-sustaining, non-localizing GDMMs should also be taken into consideration for other gene drive systems, according to their demonstrated or predicted persistence and spread.

As described for Fig. 1.3, the pathway for GDMMs may not be entirely linear, and decision-making by the community and government authorities can be anticipated to feed back into the process *(111)*. Before proceeding to the testing of first-in-class self-sustaining, non-localizing GDMMs, consideration should be given to the utility of using a self-limiting intermediate to gain experience and information that can inform RA.

1.6 Decision-making

In determining whether any GMM technology should move forward through field testing, it is expected that the responsible authority(ies) will consider criteria of both safety and efficacy for its intended use. As described in subsequent sections of this *Guidance framework*, the transition from one phase to the next will be subject to the fulfilment of efficacy (Section 2) and safety (Section 3) goals, and contingent upon regulatory and ethical approvals (Sections 4 and 5).

A new product such as GMMs should be assessed in the regulatory review process on the basis of both the benefits and risks, e.g., *(112–114)*. The primary potential benefit of GMMs would be the improvement of human health. Therefore, efficacy data will enter into decision-making regarding benefit. The stringency of efficacy demonstration required to judge a new technology worthy of moving forward may well be influenced by the potential for adverse effects associated with the technology, which in turn will differ according to the phase of testing. Variations in individual judgement, as well as the context in which decisions are being made, can lead to differing opinions about risk–benefit assessment. Some might advocate for withholding regulatory approval until absence of risk can be assured, regardless of benefit. However, decision-makers may feel that other contextual factors should also be taken into account, such as the severity of the health problem addressed by the new technology, and the availability and utility of alternative disease control methods. The meaning of “safe” is not easily defined, as it is recognized that virtually all public health products (including those currently in widespread use against diseases such as malaria and dengue) have some ability to cause adverse effects under certain conditions. With regard to genetically modified organisms (GMOs), the Nuffield Council on Bioethics has recommended that “all possible paths of action must be compared, including inaction”, recognizing that “there can be dangers in inaction, or alternative courses of action, as well as in the adoption of a particular innovation” *(115)*.

Other considerations beyond risk–benefit may come into play, especially when decisions are being made to deploy a new technology as part of the national disease control programme (Phase 4). Economic evaluations may be used to compare alternative courses of action as a basis for weighing the options and making sound decisions about the investment of scarce resources. Cost–benefit analysis involves the systematic calculation of benefits and costs in monetary terms and over time.

For public health interventions, it may be difficult to calculate the benefits of improved health in financial terms. A related method for comparing the relative costs and outcomes of multiple courses of action is cost-effectiveness analysis, which expresses benefit as a measurement of a particular health gain. For example, cost-effectiveness analysis might enable comparison of alternative malaria or dengue control regimens in terms of the costs required to achieve a particular reduction in mortality or clinical disease. Issues that will need to be factored into decision-making include whether the GMM technology will replace or reduce the need for other control measures, and, if not, how much the addition of GMMs to ongoing disease control efforts will enhance the overall effectiveness of the programme. Public health decision-makers may take a sectoral approach, comparing the cost and effectiveness of all possible disease interventions in order to select a mix that provides maximum health benefits within given resource constraints.

1.7 Critical pathway for GMMs

Proof of concept for efficacy of the GMM technology is one component of the critical path. Other key elements must be engaged to establish proof of acceptability, as well as proof of deliverability and sustainability (Fig. 1.5). Proof of acceptability involves risk analysis, regulatory approval and community/stakeholder authorization. As mentioned, the cost-effectiveness of the technology vs. other available disease control methods may influence acceptability. Proof of deliverability involves the development of an operating model with planning for sufficient technical capacity to support wider scale deployment; production capability at an appropriate scale; financing to support deployment and subsequent monitoring; methods for field-applicable high-throughput monitoring for quality control; management and mitigation capability in case of adverse events; and ongoing

Fig. 1.5. Elements of the critical pathway to GMM development and deployment

stakeholder engagement. Durability will have different implications depending on whether the GMM technology is self-limiting or self-sustaining. In either case, an important aspect will include planning the response should indications of resistance to first-generation GMMs be detected during post-implementation surveillance. As is the case for drugs and insecticides, this may require technical and financial support for ongoing research to develop next-generation products.

Challenges remain in the identification of a viable model for the development of GMMs as public health tools. Public agencies and philanthropic funders may provide the resources for early research and development. However, the level of support that will be required beyond small-scale testing may be beyond the capacity or mandate of such research funders. In the standard business model used for drugs, vaccines and insecticides (including those against malaria and dengue), industry would be expected to pick up a promising lead and provide additional financing for its development into a marketable product. However, GMMs are a new technology primarily being developed for public health use in low- to middle-income countries and their potential for direct financial returns is uncertain, especially with self-sustaining versions, which may limit industry interest. Furthermore, technology transfer to disease-endemic countries is an important goal of GMM research. Multinational consortia, public–private partnerships, non-profit corporations, and other models for broadly supported funding may provide good precedents for GMM development.

This *Guidance framework* focuses primarily on the most immediate issues to be addressed in the critical pathway to GMM development: proof of efficacy (testing for entomological and epidemiological impact) and acceptability (biosafety, ethics and engagement, and regulatory requirements).

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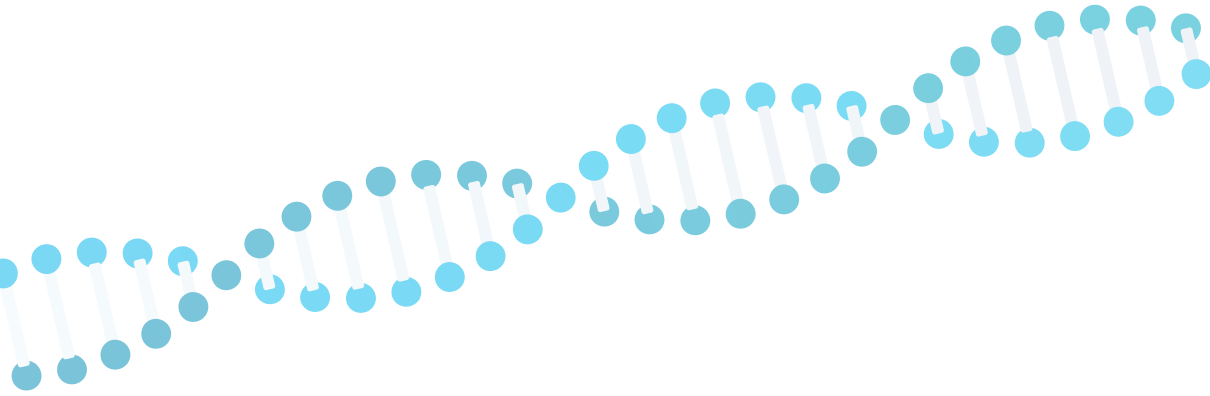

2. Efficacy evaluation

SUMMARY

Both entomological and epidemiological endpoints may be used to test the efficacy of GMMs that are intended to reduce morbidity and mortality from vector-borne diseases. The entomological endpoint is a reflection of the likelihood of disease transmission due to mosquito population characteristics, and will be the predominant outcome measure in early small-scale releases. Because this is difficult to measure directly, surrogate indicators may be chosen, which could include GMM fitness, frequency of the transgenic construct, vector population size and/or ability to support pathogen replication. The epidemiological endpoint is a measurable reduction in the incidence of infection or disease in human populations, which can be assessed in later large-scale releases. Testing for epidemiological efficacy should be conducted according to accepted standards for clinical trials. Nonlinear relationships between entomological and epidemiological outcomes may be anticipated, but entomological endpoints should be chosen with the epidemiological goal in mind. "Go/no-go" criteria for moving to the next phase of testing should be determined in advance, based on the efficacy and safety goals identified in a target product profile. Epidemiological outcomes will be detected most easily and unequivocally when trials are conducted in settings of predictable and persistent transmission, although this will not always be possible given the characteristics of different mosquito-borne diseases. Cluster randomized trials offer a powerful design for evaluating efficacy against disease transmission in field trials; however, disease transmission conditions and the nature of the various GMM systems may make other trial designs more relevant. The likelihood of significant seasonal and inter-annual variations must be taken into account in trial design. Much of the entomological monitoring required during trials and after implementation will employ commonly used methods. However, certain monitoring measures, such as phenotypic stability, will be unique to GMMs. Monitoring for ongoing disease impact may be incorporated into national disease control programmes.

It is envisaged that GMM strategies will be implemented in area-wide control programmes *(1)*. In the case of GMMs and GDMMs, such programmes are expected to be conducted over areas that may include multiple communities and contain at minimum the generational dispersal range of the target species. Area-wide vector control depends on the treatment of such large regions for success, particularly in situations where the effectiveness of the control measure will be influenced by the potential for migration of the disease vector. This implementation scale stands in contrast to interventions such as repellents or ITNs that are employed at household and individual levels. Accordingly, the scale of the testing and exposure of populations to GMM interventions has implications for how trials can be conducted. Initial studies of GMMs will take place in laboratories and large cages, but field testing will proceed through increasingly larger scale releases in which their efficacy, safety and acceptability can be assessed most realistically (Section 1, Figs. 1.3, 1.4). The purpose of any field release study should be clear prior to its initiation, and detailed experimental protocols should be developed in advance. While most GMM technologies have not yet been tested extensively in the field, experience gained from the testing of genetic sterility systems *(2, 3)* and *Wolbachia*-based strategies *(4–9)*, as well as conventional mosquito control programmes using methods such as IRS, outdoor space spraying and larviciding, can be instructive for planning efficacy trials.

This chapter focuses on three key issues of efficacy evaluation: 1) the definition of entomological and epidemiological efficacy endpoints for GMMs; 2) methodological issues and considerations related to the measurement of efficacy; and 3) empirical measures of efficacy throughout the testing pathway. The examples used focus on mosquitoes that transmit malaria and dengue (the two most common mosquito-transmitted diseases globally) because the development of GMM applications in these vectors is currently the most advanced and their biology resembles many other vector-borne disease systems. Other disease vectors may become targets of GMM control, in which case, the recommendations provided here should also prove informative.

This guidance relates to the use of GMMs to reduce or prevent transmission of mosquito-borne diseases in areas where these diseases are known to occur and therefore includes consideration of effects on incidence or prevalence of infection or disease (epidemiological efficacy). Feasible applications of GMMs that are not addressed here include those in which mosquito control authorities might want to use GMMs against the threat of vector or disease introduction. For example,

Key points

- **Efficacy testing of GMMs will begin with measurement of entomological characteristics under confined conditions, proceeding to small-scale field releases if warranted.**
- **Testing for impact on disease transmission will be conducted similarly to clinical trials in the context of larger scale GMM releases.**
- **Pre-determined performance milestones must be met for GMMs to advance from one phase of testing to the next; these will be based on the goals and characteristics of the GMMs and on the testing conditions.**

such preventive releases are used in conventional SIT programmes against Mediterranean fruit flies *(10)*. Powerful population suppression by GMM strategies could also find a market against nuisance mosquitoes in mosquito control programmes, even when disease transmission is not a major consideration. Similarly, the release of GDMMs to spread refractoriness in a population might be used to preclude the onset of disease transmission. In such cases, it would not be possible to directly measure epidemiological efficacy, and an entomological outcome of reducing frequency and scale of target species outbreaks would be the standard to demonstrate efficacy.

2.1 Efficacy end points of GMMs

The efficacy measurements of GMMs can be defined by entomological and epidemiological outcomes. These differ according to the disease, the vector species and the epidemiological circumstances. Endemic disease situations are common for malaria. As a result, the effects of interventions during trials conducted in such locations may be determined more rapidly than for dengue, which is often extremely spatially and temporally heterogeneous. These differences, as well as the occurrence of multiple vectors in one location (particularly for malaria), determine the measures of efficacy that are appropriate and feasible. Modelling based on the specific characteristics of the GMMs and current entomological and epidemiological data from the trial location will be critical for designing field trials and determining endpoints.

2.1.1 Entomological endpoint

Ideally, the goal for the entomological outcome in early field testing will be related to the desired reduction in the epidemiological outcome in later trials, although this relationship may not be linear. The relationships between parasite prevalence, infectious mosquito bites, new infections and clinical incidence can be estimated by mathematical modelling e.g., *(11–13)*.

The entomological inoculation rate (EIR) is the entomological measure of transmission, also called the force or intensity of transmission, due to mosquito population characteristics (e.g., population size, human biting rate and infectiousness). The EIR describes the degree of infection risk that a human population is exposed to for a particular disease, as determined by assessing the vector mosquito population *(14)*. In field studies, the EIR has been calculated as the number of infected vector mosquito bites per unit of time, e.g., *(15, 16)*. The EIR should be a distribution of frequencies of infectious bites over time for a range of people with different demographic characteristics in the area. A control programme is expected to shift this distribution to a lower mean frequency, but this shift might be more or less for different demographic groups.

The EIR is influenced by several factors that are specific to the geographical area, including climate, bionomics of local vectors and socioeconomic factors, as well as prevalence of infection in the human population. Accurate measures of the EIR are most easily made when the prevalence of a pathogen is high (hyperendemic disease transmission scenarios) and most difficult when the prevalence is low or in epidemic situations. It should also be anticipated that the level of disease transmission might change during trials for reasons unrelated to the trial itself, most commonly because of unusual weather that affects vector abundance. Researchers designing the trial should prepare for such eventualities by proposing variations of the protocols during the planning phase and considering the need for adaptive management during the trial (assuming this is acceptable to

regulatory authorities). In practice, EIR measurement requires analysis of field-collected mosquitoes for the presence of infective pathogens. Consequently, it can be determined only in the presence of at-risk human populations.

Given these possible limitations for directly measuring the EIR, it may be necessary to infer reductions in the EIR using surrogate indicators that contribute to the EIR, especially during early small-scale releases. Several mosquito characteristics contribute to their ability to transmit disease, and the characteristics of specific GMMs will determine the useful and feasible outcomes to measure (Section 2.6). For example, indicators of entomological efficacy might include changes in absolute density, changes in the proportion of female mosquitoes in the population, or altered propensity for feeding on humans. For GDMMs, measures of the frequency of the transgenic construct in the population will be useful. Correlation between the transgene presence and observations of the expected entomological effect can be assessed to determine the consistency and integrity of the effector phenotype. The specific characteristics of GMMs must also be considered when determining which indicators will be most useful to measure. For example, GMMs that suppress populations might have an effect in at least two ways: by allowing larval competition before the lethal effect occurs or by producing no progeny. In the former case, determining relative egg number and transgene frequency in larvae would have predictive value, but hatching rate alone would be a poor indicator since it may be close to normal. By contrast, egg number and hatching rate would be predictive for GMMs that cause complete sterility. If the GDMMs are expected to have reduced intrinsic competence to support pathogen replication, the feeding of mosquitoes using blood from infected persons in contained conditions may provide a useful indicator.

Such tractable measures can then be used to parameterize models to predict the potential effect on the EIR under various transmission conditions. Carefully measuring these surrogate indicators in early testing and integrating the outcomes into transmission models is an essential part of making efficacy predictions that will support decision-making about whether to move a GMM forward through the development pathway.

2.1.2 Epidemiological endpoint

In trials designed to prove epidemiological impact, epidemiologically meaningful effects may be measured by various means, including infection incidence, clinical disease incidence or prevalence of infection in at-risk populations. In general, trials designed to detect a decrease in the incidence of infection will be able to achieve a statistically meaningful result with a smaller cohort size than trials measuring the decreased incidence of disease, since only a subset of those infected may develop overt disease. Reduced infection incidence is generally expected to result in decreased mortality and morbidity, although in settings with highly variable transmission, this may require several seasons of observation to demonstrate. The expected contribution of the targeted vector species to disease transmission at the trial site must be taken into account in planning. Trials should be designed with durations that consider the characteristics of the intervention and its intended deployment, expected durability/residual efficacy and replacement intervals, and the epidemiology (e.g., pathogen transmission intensity) of the selected study site.

For new vector control tools in new product classes, WHO has expressed a preference for evidence from at least two well-conducted randomized controlled trials that use epidemiological outcomes and follow-up over at least two transmission seasons *(17)*. However, trial duration may be shorter (or longer) depending on the characteristics of the intervention, the study design and

the study setting *(18)*. Multi-year data collection may be especially important to demonstrate effects where disease is epidemic, highly variable from year to year, or of low prevalence. Pre-existing immunity to pathogens of interest may also influence measures of efficacy and must be considered in the experimental design.

2.2 Trial planning considerations

2.2.1 Site selection

Detecting statistically significant reductions in epidemiological outcomes will be most straightforward in areas where transmission is predictable and persistent. Therefore, trials in endemic areas are recommended. It is considered likely that a GMM intervention that is effective in an endemic area will also be effective in lower transmission conditions, although the reverse cannot be assured. Because mosquito-borne diseases are typically seasonal and variable from year to year, multi-year trials may be necessary to ensure that both low- and high-transmission years are captured by the study. Other considerations that may influence choice of trial site include the presumption that the initial testing locations for GMMs will be selected in part for their isolation (Section 1) and, for trials of epidemiological efficacy, the number of vector species present. The site where efficacy testing is to be performed should ideally have the species targeted by the GMM intervention as the predominant vector of the disease that is the subject of the trial. In situations where this cannot be accomplished, the anticipated limitations on the measurement of epidemiological efficacy must be taken into account.

Movement of mosquitoes, both through immigration of wild mosquitoes and dispersal of GMMs, can confound the interpretation of releases and prevent a positive trial outcome. When wild mosquitoes move from untreated areas into treated areas, the degree of sexual sterility or increase in transgene frequency will be reduced relative to that which would be achieved in closed populations. Therefore, effects will be demonstrated most easily when the repopulation of GMM treatment areas by untreated wild mosquitoes (and the consequent dilution of the GMM population) is minimized through strong isolating factors *(9)*. If the GMMs are rapidly self-limiting, it could be sufficient to ensure separation by 2 km, depending on the trial design *(19)*. By contrast, a self-sustaining GDMM mechanism with intergenerational effects may spread a gene well beyond the site of introduction, resulting in contamination of untreated control areas. Consequently, if self-sustaining GDMMs are being tested, separation distances must be greater in proportion to the expected rate of drive *(20, 21)*. Physical or ecological islands, and/or sufficient geographical distances between intervention and control clusters will help to prevent trial results from being confounded by inadvertent contamination. Prior field studies, including measurements of dispersal (commonly determined directly by mark-release-recapture or estimated from population genetic studies), can help to guide the selection of conditions that will provide sufficient isolation for trials of various GMM systems. GMMs that can be distinguished easily from wild mosquitoes, for example, with genes encoding visible markers such as fluorescent proteins, will aid monitoring efforts. Large-scale gene amplification technologies to detect a molecular marker are also feasible.

Movement of infected people between treatment and control areas may also confound results. In circumstances where this could be an issue, data on human movement patterns may be helpful for trial design *(5)*.

2.2.2 Ongoing disease control measures

Efficacy trials for new products should be conducted in the presence of the standard of care for disease control in the area. Field trials of GMMs are expected to take place against the background of ongoing vector and disease control programmes. The effect of these other measures on the outcomes of the GMM trials must be considered. It is neither experimentally necessary nor ethically acceptable to conduct efficacy testing under conditions in which ongoing vector control activities are discontinued. Therefore, site evaluation should be done in the presence of the same standard of care likely to be applied during the trial.

Considerable thought should be given to the phenotypes of wild mosquitoes and GMMs and the control measures that will be applied at the trial site before final site selection. It will be necessary to ensure that these other control activities continue during the trial and that they are applied uniformly across all treatment and control sites. GMMs are expected to be compatible with conventional control measures, unless those measures exploit some weakness particular to the GMMs *(22)*. For example, if high levels of insecticide resistance occur in wild populations and the GMMs are susceptible, then continued use of the specific insecticide(s) to which the wild population is resistant will disproportionately affect the GMMs and diminish or nullify their effect *(23)*. Even in cases where there is no difference in insecticide sensitivity between the GMMs and the local mosquito population, reduction in the overall numbers of GMMs at the time of release could impede their effects. To the extent feasible, researchers should plan the timing of GMM trials with information about national vector control programmes so as to avoid a situation in which insecticide application is administered at or around the same time that GMMs are released.

Attention should be given to ensuring that there are no major differences in individual human behaviour between clusters or trial sites that may affect the intervention, e.g., differences in the use of personal protection measures (including ITNs) or the domestic use of insecticides between treatment and control communities. Such differences may complicate the interpretation of GMM trial results. Information may be obtained through interviews and supplemented by direct observation (e.g., use of antimalarials, ITNs, or insecticides available in the home). A change in the use of conventional control methods during testing could change the transmission dynamics on which the trial design was based, for example, if those living in the trial site stop practising other avoidance measures because they perceive a diminished threat. Therefore, there are both scientific and ethical reasons to ensure that the trial is understood to be a research effort with no guarantee of a protective effect.

A change could also occur if an unanticipated control measure is introduced into routine use in the midst of a trial. This again emphasizes the importance of coordinating as closely as possible with the regional vector control programme during trial planning and implementation. This may be particularly relevant for trials spanning a number of years, as new control measures (e.g., vaccines or new vector control interventions) could become available, and decisions must be made in collaboration with public health officials about how such a situation should be handled. It may be necessary to introduce such new measures similarly in both treated and untreated trial sites.

2.2.3 Independent verification of results

All novel vector interventions are open to elevated critical scrutiny until their value has been demonstrated. Trials of GMMs may be controversial, and even positive results may be questioned if the research team involved is the only one to document the methods and results. Methods to ensure transparency and independent validation of results should be put in place during the trial design. Even in the early stages of field testing, research teams should strongly consider establishing an independent monitoring body to validate trial conduct and collection of results, and to protect participant safety, as is routinely the case for clinical trials *(24)*. The selection of individual(s) for this task should be based on both appropriate expertise and absence of conflict of interest regarding the trial's outcome.

An independent Data and Safety Monitoring Board (DSMB) *(25)*, including a clinical monitor, should be appointed for trials of epidemiological efficacy *(26)*. This should be a group of experts who can testify that the trial protocol has been properly followed and that relevant quality control procedures have been operating for the duration of the trial. The major responsibilities of the DSMB are to periodically review and evaluate study conduct and progress, as well as the accumulated study data for participant safety and, when appropriate, efficacy. In addition, the DSMB will make recommendations about whether the study should be continued, modified or terminated. This Board should be set up before the trial begins *(17)*. Careful thought should be given to whether a DSMB should be established for trials that do not include epidemiological outcomes. Simpler but widely accepted *(27)* alternatives (e.g., an independent monitor or an oversight panel) may be designated for entomological outcome trials to undertake particular activities that are a subset of a full trial audit, but that have adequate scope to confirm the independence and validity of results. Those chosen for this role must have sufficient knowledge to understand and analyse trial conduct and trial outcomes.

2.2.4 "Go" and "no-go" criteria

Transition from the laboratory to the field should always be planned with clearly stated performance milestones at which point the project proceeds to the next level, moves laterally to determine whether the unmet milestone is due to an artefact or experimental design issue, or is discontinued. Performance ranges can be informed by modelling the performance characteristics of the GMMs that must be met in order to achieve the desired outcome in the anticipated ecological and geographical context. Preferred product characteristics for various GMM approaches and target product profiles[3] for particular investigational products will support the establishment of clear ranges of performance that warrant proceeding with testing throughout the development pathway. The trial design will define safety and efficacy endpoints accordingly *(28)*. Researchers are advised to consult with communities at the field site, as well as government authorities, in order to understand their preferences for product characteristics when developing the target product profile (Section 4). The relevant oversight bodies should independently assess these performance standards.

There are four definite "no-go" determinations against trial continuation: 1) adverse disease transmission outcomes causally linked to the experiments; 2) unanticipated environmental harm causally linked to the experiments; 3) political or social opposition or unrest that threatens the safety of research personnel or trial participants; and 4) significant deviation of the GMMs' phenotype from

[3] Preferred product characteristics identify a core set of attributes for a general product type and are useful to provide early guidance for development of new products. Target product profiles are planning tools that identify the desired attributes of a particular product for a particular indication *(28)*.

the one intended. Safety considerations are discussed more fully in Section 3. Depending on the technology, the fourth example could include loss of sexual sterility, failure of the modification to spread to the local target species (for gene drive approaches), or high rates of failure of the intended phenotype (such as loss of pathogen refractoriness). Mitigation or remediation plans should be agreed upon with national authorities in advance of undertaking the trial.

If no negative effect on human health or environmental quality is determined to result from a trial that fails to show efficacy, the relevant national authorities and research funder should assess the value of proceeding and determine whether the project should continue. It is common for SIT programmes and vector control products to evolve methodologically during production and initial field testing, with early results falling short of the desired outcome. The technology developers may make a persuasive case that failures were due, for example, to mosquito production problems, unusual weather, or trial implementation problems. In such cases, lack of efficacy would not require a no-go decision, but it could preclude moving to the next phase until the cause of the failure is clarified and corrected.

2.2.5 Comparative efficacy between GMMs and conventional vector control

GMMs are initially being developed as complementary tools to prevent transmission of mosquito-borne diseases and, if effective, are expected to be integrated with other control methods. The effect of combinations of methods can be determined if the GMM treatment area is subject to both methods, while the control area uses only conventional vector control.

Ultimately, however, GMMs may be considered to be a substitute for some conventional vector control measures (e.g., ITNs, IRS, or larval source reduction) if there is evidence that the GMMs are effective at vector population reduction and/or preventing disease transmission, and have other valuable features such as being more cost-effective or more environmentally favourable relative to existing control measures. A non-inferiority trial aims to demonstrate that the test product is no worse than the comparator by more than a pre-specified amount. Forethought should be given to the trial design necessary to provide sufficient statistical power to detect differences. To compare the efficacy of GMMs and conventional vector control, trial design should include GMMs as one arm and conventional vector control as the other arm *(17, 29–31)*. However, the design of such non-inferiority trials must be considered carefully to ensure that the population in the GMM arm is not subjected to unnecessary risk in the absence of standard control methods. Therefore, non-inferiority trials must be justified by adequate prior demonstration of GMM efficacy.

Determining whether substitution is warranted should consider the range of potential benefits of both GMMs and the comparator control method, including not only safety and efficacy, but also cost-effectiveness and reliability. Particularly for developing countries, GMMs that are highly effective under trial conditions will be less attractive if they perform poorly when logistical, management or ecological difficulties arise, as may be more common under operational conditions. The ability to provide for the ongoing cost of the intervention should be a consideration when comparing control methods. Planning to collect the data needed for the cost-effectiveness analysis of GMMs or conventional vector control, or a combination of the two methods, should be included in the planning for trials and implementation.

2.3 Entomological efficacy studies

Progression of experiments from the laboratory to the field will require reconsideration at each stage. Specific experimental designs are likely to vary widely according to the mosquito species, the GMM approach, the study site, and country requirements. It is recommended that the validity of a specific experimental design be assessed by independent experts, such as institutional biosafety or ethics committees. The testing of entomological efficacy in the field must be determined in the context of the anticipated use of the GMMs. For example, if the anticipated use is to further reduce or eliminate populations that have been suppressed by seasonal depression or conventional methods, then the efficacy of GMMs should be evaluated in that context.

2.3.1 Surrogate endpoints for early phase testing

Entomological efficacy studies begin in Phase 1 in the laboratory, insectary or large indoor cages, and continue through field trials. Entomological endpoints should relate to the desired epidemiological outcomes *(28*). GMM strains are built for circumstances in which their potential for reducing EIR has been investigated and predicted with mathematical models *(11–13)*. These models highlight key performance characteristics that can then be measured in the laboratory to the necessary precision as a first approximation of field performance. The performance characteristics will vary with the specific strategy, but include population suppression, mating competitiveness, spread rate and frequency of the transgenic construct in a population, and expression of a particular phenotype, such as decreased vector competence or reduced reproductive capacity. Methods and considerations for Phase 1 testing of functional characteristics have been widely published *(28, 32–38)*. Measuring entomological surrogate indicators for the EIR in the field requires close supervision and dedicated well-trained staff. Sampling methods may need to be reviewed regularly. In the case of population suppression, standard entomological methods are available to determine vector abundance *(39, 40)*.

Mathematical modelling should be conducted to predict the necessary trial duration for evaluating efficacy. For GDMMs, some time may be required after the releases for the transgenic construct to reach sufficient frequency in the population for the effect to become apparent. A variety of models and scenarios should be considered, model parameter uncertainty explored, and assumptions tested. During the course of field trials, experimental outcomes can be used to refine the parameters of the intervention's computational models or to add relevant monitoring parameters noted to be important. These changes may result in alterations to the trial design or expected outcomes. Data from the trial will be useful for evaluating model performance to determine whether its predictions are validated by trial observations. Stakeholders and regulators should be clearly informed on how updated model predictions may affect trial conduct or continuation.

2.3.2 Influence of seasonal and inter-annual variations on trial design

It is common for there to be seasonal and inter-annual variations in climatic conditions and other intervention measures that affect vector abundance, species composition, transmission intensity and disease incidence. All field trials must take these variations into consideration in order to ensure experimental success and enable the results to be generalized.

A reduction in population size observed in a short-term trial of population suppression technologies could be a fortuitous characteristic of a specific season alone, but one that might not be repeatable or lasting. Multi-year evaluations would provide more robust assessments of both the climate and co-intervention effects, and give an idea of how the intervention effect may vary as a function of annual medium-term variations or variations in the efficacy of the construct. Ideally, baseline entomological data will also be collected at the field site over multiple seasons to underpin the trial design *(21)*.

2.3.3 Nonlinear relationships between entomological and epidemiological outcomes

Reductions in vector abundance or increases in refractory transgenes to a high frequency should in most cases lead to reduced EIR, but this relationship can be complex. In the case of malaria in hyperendemic areas, reduction of disease occurs only when the EIR falls below a threshold necessary to maintain transmission, often cited as one infective bite per year *(15)*. For dengue, reduction of vector abundance alone does not necessarily translate directly into reduction of incidence, as transmission has been observed in the presence of low apparent numbers of mosquitoes *(41, 42)*.

For GMM systems intended to reduce female fertility, the simplest outcome to measure is a direct measure of the number of larvae produced per female. This measurement can be taken by obtaining eggs from blood-fed field-collected female mosquitoes or by hatching eggs collected from outdoor ovitraps. While it may seem obvious that increasing sterility would lead to a reduction of adult populations, there is seldom a direct relationship due to the dynamic nature of larval competition. Negative density dependence[4] *(43, 44)* is common and tends to dampen the initial effects of reduced fecundity on adult population sizes. These interactions mean that different population suppression systems aimed at reducing female fertility will perform differently, depending on whether females are sterile or larval competition is maintained *(45, 46)*. In some circumstances, over-compensation[5] may also cause increases in the adult population size when larval density decreases. Both of these effects occur due to competition for food in larval sites. Knowledge of the population dynamics as determined by larval abundance would be a useful predictor of the reproduction reduction necessary to realize particular levels of population suppression. This knowledge could be gained through ecological studies prior to releases in order to determine the characteristics of larval breeding sites.

2.3.4 Entomological monitoring unique to GMMs

For producing GMM stock to be used in field testing, reproducible life history and phenotype can only be expected if the mosquitoes are reared and maintained using standardized procedures. GMM production should utilize standard operating procedures (SOPs) and other quality management and good manufacturing practices *(47, 48)*.

Most of the characteristics used to monitor GMMs' functionality are not unique to the technology. Methods to evaluate these characteristics during field testing have been developed and used routinely to gather entomological data *(40, 49)*. These include determining adult abundance, host preference, and/or the ability to develop and transmit parasites or viruses (vector competence).

[4] Population regulation in which increased population density reduces its rate of increase. In this case, adding more immature individuals to a population does not proportionately increase the number of adults.

[5] Population regulation in which reductions in some stage of the population actually increase population size, e.g., by improving survival to adulthood.

These and other biological characteristics should be catalogued thoroughly during GMM testing. Some properties are, however, particularly relevant for describing and predicting the entomological efficacy of GMMs, as well as for RA (Section 3).

Molecular properties

A thorough description of the GMMs includes the transgenic components, genetic background and novel phenotype(s). This description enables initial assessment of the GMM itself and observations of changes in its salient features, including the transgenic construct, its insertion site and strain background. The description of the GMMs should include information about the strains that have contributed genetic material.

Phenotypic stability

Genetic changes that will affect efficacy can occur within the GMM line or within the target mosquito population in the field. Among the few characteristics of GMMs that are unlike those monitored for typical entomological surveys, phenotypic stability is paramount and is a strong determinant of efficacy. This can be evaluated by answering several questions: Does the mosquito exhibit the desired characteristics over multiple generations in both laboratory studies and field studies? If the phenotype is not fully penetrant[6] but the transgenic construct is stable, what effect on its efficacy and fitness do models predict?

It will be possible to measure stability in increasingly realistic trials as the GMMs move forward through the phases; however, the process should begin with observation in the laboratory and, as utilized, indoor population cages (Phase 1). Methods for testing variations in expression of a transgene should be tested so that significant deviations in novel environments can be identified. It is particularly important to determine whether the phenotypes that have been measured in stable laboratory environments are consistent when, for example, temperature variations are experienced. Similarly, laboratory evaluations should include transgene expression in aged individuals and in a variety of genetic backgrounds. If expression of the phenotype is conditional on some environmental factor, the effects of variation in the presence of that factor should be examined.

Under field conditions, there will be an increase in the genetic diversity of the mosquitoes and pathogens with which the GMMs interact, and greater environmental variation. Observation for such effects should be intensified during isolated small-scale releases when unanticipated events can be restricted in time and space. Such measurements should continue in later stage trials, as well as periodically in the context of post-implementation surveillance.

Resistance could develop as a result of mutations in the transgenic construct or in the target mosquito population; when this could interfere with efficacy or the ability to track the transgene, it must be monitored. This is especially relevant for GDMMs after extended persistence and can result from selection of an existing variation in the population or an arising mutation *(50, 51)*. As with resistance to insecticides, the potential for mutations to arise will be difficult to predict with high certainty from small laboratory studies. It is possible, however, to look for the presence of pre-existing variants in the wild mosquito population that are likely to result in resistance *(28)* and to target conserved sites in the mosquito genome *(52)*. It is not simply the appearance of

[6] The transgene phenotype is predictably absent in some proportion of the individuals in a population, despite the transgene being present in an unmodified form in all individuals.

resistance, but an increase in its frequency that may decrease the usefulness of the intervention. Such resistance events would be expected to become more evident in the later stages of field testing, and monitoring should continue throughout the development pathway. The likelihood of such resistance arising and its consequences should be considered thoroughly in RA (Section 3). Measures should be put in place as part of the development plan to prevent or delay (if possible), detect and respond to such resistance *(28)*.

The pathogen also has the potential to develop mechanisms for evading the refractoriness of GMMs in the case of population replacement strategies. Therefore, the refractoriness of GMMs to the target pathogen should be monitored throughout the testing pathway for these strategies *(21, 28)*.

Fitness

The fitness[7] of transgenic mosquitoes has been the subject of much study and discussion *(32, 53–58)*. While this is a characteristic relevant to long-term population trends, it is of less relevance to GM-sterile and non-driving population suppression strategies, since in these cases the GMMs have reduced fitness by design. What is relevant is their ability to suppress wild populations and, for GMMs intended to have a multigenerational effect, the duration of the suppressive function. One measure of the maximal rate of effect on population suppression is the mating competitiveness value *(59)*, which indicates (usually on a 0–1 scale) the relative frequency of mating of a male in question (in this case, a GMM) when in competition with a reference wild type male. However, there is no absolute value of competitiveness that precludes the use of a strain, since even very low-value insects (e.g., 0.2 for Medfly) can effectively suppress populations if sufficient numbers are released. Nonetheless, measuring competitiveness, longevity and the duration of effect will provide indices to determine the necessary scale of releases and their efficiency. Such indices are, therefore, important for strain efficacy evaluation and estimations of delivery requirements.

Fitness may be more critical for GDMMs. The desired effect is the introgression of a transgenic construct causing a phenotypic change in an otherwise wild mosquito population. After release, the introgression rate will be determined by recombination between the transgenic construct and the wild genome (at rates determined partly by the presence of natural inversions and homologous pairing) and the drive rate of the construct. Therefore, the fitness of repeatedly out-crossed mosquitoes must be measured. Assuming that the transgenic construct contains a drive system, the loss of fitness and reduction in gene frequency due to the transgenic construct must be balanced with the super-Mendelian inheritance rates[8] conferred by the drive mechanism (Section 1). Models can be used to predict the ranges of fitness and drive that will permit appropriate spread of the transgenic construct. When a self-sustaining gene drive system is implemented to achieve population replacement, the frequency of the functional gene in mosquito populations into which the GMMs have been released is the ultimate measure of this balance. Measures of the spread of the gene drive construct in laboratory or indoor cage testing can be used in modelling to refine efficacy predictions. These will be enhanced by the introgression of the transgenic construct into the wild type genetic background. Phase 2 studies will begin to examine the effects of other variables.

[7] Fitness is equal to the average contribution to the gene pool of the next generation that is made by individuals of the specified genotype or phenotype.

[8] An individual heterozygous for a transgene will produce progeny that are approximately 50% transgenic in a normal non-drive system. Super-Mendelian inheritance is expected in drive systems, and these individuals produce > 50% transgenic progeny.

2.4 Epidemiological trial design

Before entering into testing for epidemiological efficacy, researchers should understand as much as possible about GMMs' behaviour from prior releases, as this knowledge will contribute to efficient trial design. This may require multiple small-scale releases to collect data under different ecological conditions and delivery schemes. The cluster randomized trial (CRT) *(60)*, in which groups of people are evaluated (as opposed to individuals), is a powerful design for detecting the efficacy of GMM applications when an epidemiological outcome will be measured *(20)*. However, other trial designs can be considered *(17, 18)*. Although adaptive trial design introduces complexity *(61)*, it may be important under some circumstances, such as when testing GDMMs where characteristics of persistence and spread must be considered *(21)*. Longitudinal studies with enrolled cohorts are recommended. Active case detection, whereby participants are contacted on a regular basis, is preferred whenever resources are available, since it maximizes the detection of infections or clinical cases. The most accepted malaria *(62)* and dengue fever *(63)* case definitions should be used. Good Clinical Practice (GCP) should be followed (Section 5.3.4) *(64)*.

2.4.1 Special considerations for dengue interventions

Where regional dengue transmission is due to a single vector species, vector elimination may be proposed as the efficacy measurement if GMMs are effective in achieving and maintaining local elimination of that vector. However, determining the threshold of vector abundance reduction required to achieve significant reduction in dengue disease incidence requires epidemiological modelling and empirical studies (Section 2.3.3). Such threshold vector densities may vary between geographical localities. In the case of GMM population replacement strategies, it may be necessary to measure infection or disease incidence reduction in intervention areas relative to untreated control areas in order to provide high confidence in efficacy. It should be noted that WHO recommendations require demonstration of public health value, necessitating the measurement of epidemiological outcomes *(18)*.

Since dengue transmission is highly variable, it is possible that trials will need to be conducted on large spatial and temporal scales, with large numbers of clusters, in order to detect an epidemiological effect. Large reductions of normally high transmission could be easily measured. More typically, even a GMM trial that completely eliminates transmission may need to extend over multiple seasons in order to provide sufficient statistical power to conclude efficacy. GMM technologies are designed to reduce the likelihood of transmission for people within the area under management, rather than to treat individuals within it. Thus, the possibility that individuals are being exposed routinely to unknown risk of infection when travelling outside their respective control or GMM treatment area must be considered in trial design, as this could confound the interpretation of results. Trial planning should consider methods to enable identification of individuals who become infected outside of the trial area so that their contribution to incidence can be discounted. Examples of trial design for other dengue control technologies are available *(4–8)*.

Given the expected heterogeneity of transmission, the likely approach to assessing epidemiological impact will be to measure indicators of infection in individuals presenting with febrile illness or clinically suspected dengue *(5, 65)*. In acute infection, viraemia can be determined using serologic or nucleic acid amplification tests for dengue non-structural protein 1 in blood samples *(66)*. The

presence of anti-dengue antibodies, as detected by plaque-reduction neutralization assay, can also be indicative of recent infection *(67, 68)*. The need to evaluate impact on the four different dengue virus serotypes must be kept in mind. Molecular detection of dengue virus in mosquitoes could provide an additional useful tool for predicting the epidemiological outcome *(69)*.

2.4.2 Special considerations for malaria interventions

While epidemiological outcomes will likely be relatively easier to measure in malaria-endemic settings, methods may differ according to whether trials take place under conditions where there are still appreciable levels of transmission (malaria control settings) or under conditions where disease burden and transmission are low (such as malaria elimination settings) *(70, 71)*. In malaria control settings, the primary clinical endpoints are expected to be reduction in the incidence of infection in children or incidence of disease *(17)*. Determination of infection incidence may require treatment to clear parasites at the start of the trial so that new infections can be detected. Secondary clinical endpoints might include changes in anaemia or parasite diversity *(21)*. In malaria elimination settings, where large populations may be required to ensure sufficient accrual, it may be necessary to look for reduction in infection incidence in all age groups.

Efforts must be made to find trial venues that satisfy the RA requirements and provide control sites matched for human demographics and disease patterns. Prior studies and modelling should be conducted to obtain insights into how seasons and ecological conditions at the site could affect the performance of GMMs and influence epidemiological outcomes. For example, preliminary field studies or historical records may reveal the contributions of individual vector species to the overall disease transmission levels. However, interpretation of epidemiological outcomes by GMMs in multi-species sites will require caution. While these are often considered additive, each species' contribution may not conform to such a simple relationship, especially when one key vector species has a much higher efficiency (vectorial capacity) than others. Furthermore, there is a possibility that the suppression of one target species could result in an increase of other, closely related vector species (Section 3). Such issues should be anticipated as early as possible and factored into the choice of target species in GMM design, as well as selection of trial sites when entering into field testing. If the GMMs target only one of several vector species at the trial site, epidemiological endpoints must be established accordingly. For population replacement strategies, the susceptibility of diverse locally circulating parasite strains must also be considered.

Several methods are available for malaria diagnosis *(72)*. Historically, the "gold standard" has been microscopic examination of blood smears *(73)*. However, rapid diagnostic tests (RDTs) have become increasingly preferred. Many malaria RDTs are available commercially from several manufacturers *(74)*. The specificity of these tests varies: Some can only detect *Plasmodium falciparum*, while others can also detect non-*P. falciparum* infections. RDT performance can vary under different conditions, and both false-negative and false-positive results have been observed *(75)*. The specific RDT for malaria diagnosis used in a trial must be carefully selected and thoroughly evaluated according to WHO guidelines. Highly sensitive detection methods may be required for trials conducted in malaria elimination settings.

2.4.3 Special considerations for GDMMs

Careful advanced planning will be required for GDMMs because the degree of persistence and spread of the modification, and possibilities for dispersal of the GDMMs will influence trial design *(21)*. The potential for driving transgenes to appear in mosquito populations in control sites before the end of the trial must be considered. Buffer zones (neutral areas between treatment and control sites) may help to prevent or slow cross-contamination *(20, 60)*. Information on the rate at which the modification is expected to spread into the local mosquito population (from predictions based on contained studies or observations from earlier small-scale releases) will help to predict the necessary size of such buffer zones. A stepped wedge design *(76)*, with sequential roll-out of GMMs across sites, might address this issue; other designs are also possible.

Another complexity in assessing the efficacy of GDMMs is related to when to begin measuring the effect on infection or disease incidence. The fewer GDMMs that are released, the longer it will take for the modification to spread throughout the mosquito population at the treatment site. If the drive spreads slowly, beginning measurement of epidemiological impact too early could result in an underestimate of the GDMMs' effect. If, however, the modification spreads rapidly and substantially reduces the incidence of infection or disease, it might be possible to measure change across the leading edge as the modification moves through the population. Again, information on the rate at which the modification is expected to spread spatially, collected from earlier studies, will be valuable for planning.

The design of monitoring plans must take into account the expectation that the GDMM system may spread beyond the initial release site, as informed by modelling. Monitoring requirements for GDMMs should be agreed upon by developers, regulators and stakeholders at the trial site before field testing begins. Safety monitoring may need to continue for some period after efficacy testing is completed (Section 3).

2.5 Implementation and post-implementation surveillance

GMMs that reach Phase 4 will have undergone extensive efficacy testing. Their behaviour in a variety of natural settings will be established by Phase 3 activities. The intervention at this point is no longer experimental, but is a control measure whose ongoing effectiveness in a public health programme is being determined. Implementation as a public health tool will involve a more extensive and systematic regional deployment design, based on Phase 3 observations, in order to maximize success. Implementation strategies must take into account the characteristics of the GMMs, population size of the target mosquito species, mosquito movement, and geographical and climatic factors. Implementation plans must consider production and distribution requirements and may continue to be refined to increase efficiency with additional experience. Implementation is expected to be under the purview of national control programmes, which may undertake the activities directly, but other models are also possible.

It cannot be assumed that GMMs will continue to be effective indefinitely. Analogous with the implementation of insecticides for ITNs, IRS and larviciding, or drugs used for chemotherapy, efficacy can change due to changes in the genetic constitution of the mosquitoes or the pathogen, as well as due to external factors such as weather and human activities. Consequently, there will

be an ongoing need for post-marketing evaluation of effectiveness and safety (Section 3). This will require standard entomological monitoring assessment, such as larval/adult abundance and vector infection rate, and should be considered in the context of routine monitoring conducted by national vector control programmes. For GDMMs, additional measurement for presence of the transgenic construct will be required. Ongoing monitoring of epidemiological effectiveness may be integrated into national disease control and elimination efforts. Molecular xenomonitoring may prove to be a useful surveillance method *(77)*. As with other vector control tools, it will be important to provide a pipeline of next-generation GMM products should loss of effectiveness be detected.

2.6 Efficacy measurement at different testing phases

Efficacy measurements will vary depending on the intended effects of GMM strategies and the testing phase. Only entomological outcomes can be determined under physical confinement and in small-scale releases, but entomological endpoints should relate to the desired epidemiological outcome as predicted by modelling. It is expected that measurements of epidemiological outcome will not be undertaken until entomological outcomes clearly indicate the potential for reduced transmission.

Typical measurements and designs that should be considered to determine efficacy will evolve throughout the GMM development pathway. The prioritization of various activities is likely to change as experience and knowledge about performance characteristics in diverse settings are gained.

2.6.1 Phase 1 – Laboratory and population cage studies

This phase will include development of a target product profile that defines the minimum essential efficacy characteristics that must be met to progress the GMMs through the development pathway, as well as optimal efficacy characteristics for the ideal GMM product. Initial cage testing will likely involve GMMs in the genetic background of a laboratory strain of the target mosquito species, and be conducted in the absence of other control methods and under conditions that optimize the potential for success. Later in Phase 1, it will be desirable to test the capabilities of the GMMs introgressed into the genetic background of wild mosquitoes at the future field site,[9] to the extent possible; such testing may need to be done in facilities located at or near the intended field site.

Conventional experimental approaches can be used to directly compare GMM cages and control cages housing unmodified mosquitoes of the appropriate genetic background, with random intervention assignment. Only entomological measurements can be made and, thus, the primary objective should be the potential for reducing transmission intensity, as indicated by the surrogate endpoints described above. A sufficient number of replicates should be used to detect the expected difference in the entomological outcomes between the GMM and control cages. Although not considered a requirement, testing in large environmentally controlled indoor chambers, which enable examination of the effect of variations in light, temperature, humidity and mosquito density, may be helpful for predicting field performance, and thus for making go/no-go decisions about moving to field testing and for designing subsequent field studies.

[9] "Wild" refers here to a colony of mosquitoes isolated recently from the target population or a sample actually collected from natural populations and used without colonization. Such colonies are genetically more similar to natural mosquitoes than highly inbred laboratory strains.

2. Efficacy evaluation

Activities at this phase include:

- establishment of efficacy and other goals in a target product profile;
- basic description of the transgenic construct, including its sequence, insertion site, phenotype and inheritance; this information will be important for regulatory review and can be used during field testing and post-implementation surveillance to confirm the GMMs' characteristics (Section 3);
- measurement of:
  - stability of the transgene and its phenotype, including variation in expression of any effector and the marker;
  - other life-history characteristics pertinent to both efficacy and safety (Section 3), including adult longevity, mortality rate, egg numbers and hatching rate, larval-to-pupal and pupal-to-adult survival;
  - mating competitiveness against comparator mosquito strains, which may be standard laboratory strains or recently laboratory-adapted from wild populations;
  - frequency of GMMs that express the desired characteristic and the level of expression;
  - for GDMMs, rate of spread of the transgenic construct in cage populations, off-target effects and development of resistance;
  - for population replacement strategies, capability to host and transmit the targeted pathogen(s);
  - for population suppression strategies, rate of population reduction in laboratory cage trials;
- modelling of effects anticipated in wild mosquito populations and predicted effect on disease transmission;
- measurement of the insecticide susceptibility profile compared to the wild population;
- establishment of, and training on, the SOPs for GMM production and Phase 2 testing.

Modification with self-sustaining, non-localizing gene drive systems introduces additional complexity for decision-making at the end of this phase *(21, 28)*. The possibility that escape of only a few of these GMMs could theoretically result in the modification becoming established in the local population of target mosquitoes must be taken into account when making the decision to move to initial field testing and seeking regulatory approval to do so *(78, 79)*. While this decision will be based primarily on safety characteristics (Section 3), it has been recommended in this case that evidence of resistance arising too rapidly to predict a beneficial epidemiological effect should be considered a "no-go" efficacy criterion for moving GDMMs forward to field testing at any level *(21)*.

2.6.2 Phase 2 – Confined field studies

Baseline studies of vector composition and abundance at field sites should begin early enough to obtain the multi-seasonal entomological, epidemiological and ecological data necessary to design field trials. In preparation for Phase 2, an independent monitor or oversight committee should be established to verify methods and results. It is generally recommended for all field testing that the transgenic construct be introgressed into the genetic background of the local target mosquitoes. This is expected to increase GMM compatibility and mating competitiveness under field conditions, while also minimizing the introduction of non-native alleles into the local population of target mosquitoes.

Physically confined, or contained, field testing (sometimes termed semi-field testing) can be performed in large outdoor cages that provide physical barriers and special procedures to prevent escape (Section 1). Such confinement is intended to enable observation of GMMs under more natural conditions, while still limiting release into the environment. Ecologically confined refers to testing conducted in delimited areas that provide some ecological or geographical isolation to reduce the possibility of inward or outward mosquito migration. Regulators will determine whether both types of testing are necessary, a decision that may be influenced more by safety than by efficacy considerations (Section 3).

Entomological activities in outdoor cages include:

- measurement of:
  - mating competitiveness against mosquito strains having a wild genetic constitution under more natural conditions;
  - frequency of GMMs that express the desired characteristic and the level of expression in strains containing wild genetic background;
  - for GDMMs, the rate of spread of a transgene in cage populations containing wild mosquito isolates and comparison with Phase 1 predictions;
  - egg-hatching rates and other pertinent life-history characteristics in crosses to wild mosquitoes;
  - for population suppression strategies, the rate of population reduction when introduced into populations of wild mosquitoes;
- for population replacement strategies, removal of GDMMs from the outdoor cage to suitable indoor containment facilities to test their ability to host or transmit local pathogen isolates may be possible;
- GMM release simulations.

Entomological activities in initial small-scale field release include:

- establishment of efficacy endpoints prior to the study;
- establishment of intervention and control sites with similar entomological, epidemiological and ecological characteristics;
- measurement of:
  - GMM dispersal;
  - for GDMMs, the rate of spread of a transgene in wild populations and comparison with predictions from earlier caged studies;
  - functionality and mutation rate of the transgenic construct;
  - for population suppression strategies, reduction in the wild mosquito population at intervention site(s);
  - for population replacement strategies, the ability to sustain development of local pathogen isolates as an indication of potential for transmission;
- observation of compatibility with other mosquito control measures;
- model refinement based on field observations and estimation of impact on the EIR;

- refinement of efficacy goals in the target product profile;
- establishment of and training on SOPs for GMM production and release in Phase 3 trials.

Epidemiological activities in initial small-scale field release might include:

- comparison of disease incidence data before and after release and/or between control and intervention sites by passive surveillance at local clinics and hospitals to screen for preliminary indications of efficacy as well as safety (Section 3).

2.6.3 Phase 3 – Staged open-field releases

Before planning large-scale releases to measure epidemiological outcomes, multiple small-scale open releases will likely be needed to understand the delivery requirements and functionality of GMMs under different circumstances, such as different ecologies, mosquito demographics, seasons, and levels of human habitation. Complex large trials should only begin after this information is at hand, as it will be necessary for trial design and interpretation. Preparation for open field releases will require baseline studies of vector composition and abundance at the trial sites.

Entomological activities include:

- observation of compatibility with other mosquito control measures;
- measurement of:
  - the EIR when possible;
  - functionality, phenotypic stability and mutation rate of the transgenic construct;
  - GMM dispersal;
  - for GDMMs, the rate of spread of a transgene in wild populations and comparison with earlier model predictions;
  - for population suppression strategies, reduction of wild populations at intervention sites;
  - for population replacement strategies, native pathogen development and transmission in progeny from natural mating of the GDMMs to wild mosquitoes;
- model refinement and validation based on field observations;
- development of methods for measuring or estimating GDMM frequency and cross-species gene transfer, and consideration of how long these activities should continue post-trial (Section 3);
- development of implementation plans, including scale-up manufacturing, delivery and post-implementation monitoring of entomological indicators.

Epidemiological activities include:

- description of epidemiological efficacy trials in a public registry, as with other types of clinical trials *(80)*;
- development of plans for post-trial and post-implementation monitoring of epidemiological effectiveness indicators, including how long these activities should continue;
- measurement of incidence/prevalence of infection or disease during intervention trials.

2.6.4 Phase 4 – Implementation and post-implementation

Implementation as a public health tool will consist of the broader and more systematic delivery of GMMs, according to the characteristics of spread and persistence observed in Phase 3. The deployment of self-sustaining GDMMs at scale as a public health tool will likely build on and expand Phase 3 releases.

Like any public health intervention, GMMs will require ongoing monitoring to determine whether their effectiveness has diminished with time or unexpected effects have become evident upon widespread use or use in new areas. Appropriate measurement of the entomological and epidemiological outcomes that guided deployment of the GMMs must be continued after the trials cease. Depending on the type of GMM technology and the deployment strategy, multi-year follow-up may be required.

A subset of the entomological and epidemiological outcomes that were measured during field trials should be monitored in order to determine whether the positive effects on vector and human populations are sustained (Section 3). As the GMMs become deployed over large areas, this monitoring will likely be integrated into existing national disease control or elimination programmes. If a loss of efficacy is noticed – similar to the appearance of resistance with conventional insecticide-based control – any next-generation GMMs must also be tested and monitored as described above. Forethought should be given to when such new tools may be needed so that they may be approved and ready for use.

Entomological activities include:

- wide-scale intermittent measurement of presence and spread of the transgenic construct;
- widespread intermittent sampling of the functionality and mutation rate of the transgenic construct;
- for population suppression strategies, sampling of vector abundance;
- for refractory GMMs, observation of native pathogen development in mosquitoes collected in disparate settings;
- model refinement based on entomological and epidemiological observations.

Epidemiological activities include:

- longitudinal passive case detection of the targeted disease and other mosquito-borne diseases as required by authorities for effectiveness or safety monitoring, which might be based on routinely collected case reports and conducted under the auspices of the relevant national control programme.

2.7 Co-development and capacity strengthening

Conducting successful trials and implementing GMM interventions will require strong intellectual understanding, cultural understanding and logistical capabilities in locations where these technologies are under consideration. The breadth of activities described above require personnel and laboratories prepared to perform medical, epidemiological, entomological and ecological studies. Further sub-specializations will be required: medical entomology, molecular biology, statistics and diagnostic analysis, to name a few. It is both undesirable and impossible for these capacities to be supplied without reliance on well-trained national personnel. Moreover, as discussed elsewhere in this guidance, in-country teams will play an essential role in all regulatory and engagement activities.

When Phase 1 research occurs somewhere other than where field testing will be conducted, partnerships with local in-country scientists and institutions must begin early in the development process and be conducted in a spirit of co-ownership and co-development of the technology. If an appropriate containment facility is not available at the partner site, or risk of escape from containment is not deemed acceptable, the initial work with GDMMs may need to be done outside the region. However, scientists from the partner institution(s) should be involved in this work.

An explicit personnel plan for the project should include the specific types of supporting expertise that will be required and the degree to which the project can and must engage national capacities. When specific abilities are lacking, a strategy for training national personnel to satisfy these needs should be planned and undertaken. Sufficient lead time for training must be part of the development plan. A commitment to retain trained personnel in the trial will be important for ensuring continuity and enabling deep understanding of and involvement in the project. This plan should include consideration of how national disease control programme staff can be incorporated into testing, implementation and post-implementation activities, and any associated needs for technical capacity strengthening.

For many national staff, training opportunities will be professional highlights that may make them eligible for national positions of authority and responsibility. With their knowledge of personnel, technologies, and national regulatory and political avenues, they will constitute invaluable long-term national focal points for the research and development of future potential novel interventions. Commitment to providing assistance for training lays a foundation for the future strength and independence of national research activities.

Capacity includes facilities. Even though the construction of major facilities will be beyond the resources of small trials, strengthening the capacities of facilities can include providing the scientific equipment, computers and software required for the trials, and making necessary improvements in biosecurity to achieve risk mitigation goals. Some structures, such as physical confinement (containment) facilities, will be so specialized that support for their construction will likely come from the trial programme or in combination with other studies that could capitalize on the existence of a multi-purpose facility. These kinds of facilities can be used to perform studies on mosquito behaviour, life history and non-GMM interventions. Coordinating investment in their construction provides a long-term foundation for wider sustained trials of vector interventions and research activities. Mechanisms for regional coordination should be encouraged.

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3. Safety evaluation

SUMMARY

Safety in the development of GMMs focuses on reducing any possible adverse effects on health and the environment to acceptable levels, keeping in mind the known and ongoing adverse impact of vector-borne diseases. Risk analysis, a multi-stage process for identifying and managing potential problems, helps to achieve an appropriate level of safety. RA of GMMs should determine the potential hazards and mechanisms of harmful impact on the receiving environment, human or animal health; the likelihood and magnitude of that harmful impact; and the levels and consequences of uncertainty associated with these effects. RM should provide appropriate measures to reduce risk to an acceptable level. Both RA and RM should be grounded in a country's health, environmental and biodiversity protection goals, also taking into account any additional community concerns. Risk communication should ensure that there is stakeholder input on and well-documented understanding of what risks have been identified, how they have been assessed, how RM will be implemented and whether the level of risk is acceptable. Once development moves to the implementation phase, risk analysis for GMMs should be embedded in a broader benefit–risk deliberation. Benefits and risks may be considered in various types of impact assessment, which can include consideration of both positive and negative socioeconomic, health and environmental effects.

RA must be conducted on a case-specific basis, taking into account the characteristics of the GMMs, their intended use and the receiving environment. A phased development and testing pathway for GMMs helps to ensure that RM measures are proportionate to the level of risk at each phase. Observation of GMM characteristics and behaviour under physical confinement within the laboratory or indoor cages, coupled with computer simulation modelling, provides an opportunity to estimate the likelihood and impact of hazards for which little or no empirical data exist at that stage. Further testing phases supply data to reduce uncertainty in the assessment of health and ecological effects under increasingly realistic conditions of exposure. The characteristics of certain GDMMs may make it difficult to delineate distinct cutoffs between phases in the testing pathway beyond the initial physically confined studies. This may make the data relevant to RA obtained in Phase 1 a major driver for the decision to proceed to field testing. As testing moves through the development pathway, the choice of appropriate risk comparators changes depending on the particular risk being examined.

All GMM products will undergo RA as an element of the regulatory and decision-making process. This risk-based biosafety evaluation focuses on the potential for harm to relevant protection goals, such as safety for the natural environment and human or animal health. Some have called for a broader technology assessment approach, which moves beyond standard RA to consider socioeconomic and cultural impact assessment, and the appropriateness of the technology to achieve the stated goal compared to other available methods *(1)* (Section 3.10). The risk of novel GMM interventions can therefore be considered in the context of need, which includes the substantial ongoing mortality, morbidity and economic burden of vector-borne diseases, even in the presence of current control measures, as well as widespread calls for development of new vector control tools (Foreword and Section 1).

3.1 Risk analysis

The concept of risk takes into account both the likelihood and magnitude of harm arising from an identified hazard (an unwanted or adverse event that could have a negative impact or cause harm). Risk analysis is an objective process to identify what hazards are relevant, how significant the risks are, how the identified risks can be managed, and how both the risks and their management can be communicated effectively to all concerned. Risks should be examined and responded to through established protocols within a risk analysis framework, as described by international standards and national policies on environmental and human health risks and their acceptability

Key points

- **Risk analysis frameworks used for other technologies provide useful precedents for the risk analysis of GMMs.**
- **Risk analysis of GMMs focuses on evaluating the potential to cause harm with respect to relevant protection goals, such as health and the environment, and should be conducted before each new phase of testing; risks should be considered in the context of appropriate comparators.**
- **RA and related RM must be conducted on a case-by-case basis, focusing on the particular GMM system, receiving environment, and objectives within the phase of testing under evaluation; the goal is to achieve a level of safety considered acceptable by decision-makers and other stakeholders.**
- **Opportunities for consultation with and input by relevant stakeholders are included in the risk analysis and impact assessment processes.**
- **Safety oversight will be provided at multiple levels, including by national regulatory authorities and institutional or national committees dealing with ethical and biosafety issues, as well as by external groups such as a DSMB for studies on disease impact; international and regional agreements may also be applicable for GMMs anticipated to cross national boundaries.**

or management. The development of earlier GMO and biocontrol technologies provides useful precedents for risk analysis of GMMs *(2–9)*. Experience with releases of biological control agents provides additional relevant insights into how the potential for transboundary movement may be managed (Section 5.3.6) *(10)*. Furthermore, there are analogies with biosafety management associated with the release, use and environmental exposure to vaccines or medicinal products based on GM viruses or bacteria that may be informative *(11, 12)*.

Risk analyses must be undertaken on a case-by-case basis to identify and manage any unacceptable adverse effects on the environment and/or health that may arise from a particular set of actions or events. In countries with defined environmental policies, the laws undergirding them derive from a consideration of the nation's values and protection goals, which provide the framework for determining acceptable risk levels.

Risk analysis for GMOs follows a multi-stage process (Box 3.1).

Box 3.1. Components of risk analysis for GMOs

Problem formulation is part of the planning activity that precedes the risk assessment. The goal is to formulate the scope of the risk assessment to assure its relevance for decision-making. This begins with identification of the protection goals that may plausibly be impacted by the GMO. Specifying the "problem" in its entirety, along with all assumptions, is key to its sound formulation. This is a critical first step that greatly affects the acceptability and credibility of the assessment that follows.

Risk assessment (RA)

1. **Hazard identification determines any adverse impact on the stated protection goals that might result from the novel genotypic or phenotypic features or properties of the GMO.**
2. **Exposure assessment evaluates the level and nature of exposure to the identified adverse events that is likely in the intended receiving environment.**
3. **Hazard characterization evaluates the consequences of the adverse events being realized.**
4. **Risk characterization estimates the overall risk posed by the GMO to the protection goals under the described conditions of use, based on the likelihood and consequences of the adverse events being realized.**
5. **Risk report is a recommendation summarizing the findings and conclusions of the RA as to whether the risks are acceptable or not and identifying risk management strategies.**

Risk management (RM)

RM may be enacted in the case that risk is considered unacceptable. RM seeks to identify options and actions that can avoid or reduce to an acceptable level any identified risks.

Risk conclusion

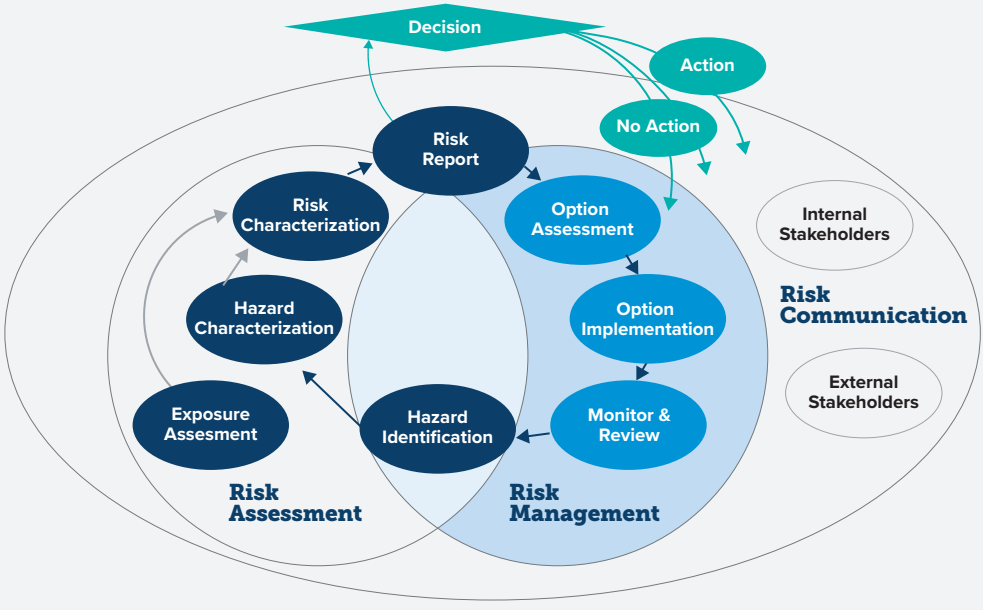
The prior stages lead to decision-making by national authorities (Section 5) and involved communities or other stakeholders (Section 4) about the acceptability of the proposed action, taking into account any residual risk remaining after feasible RM as described in the risk report, and the acceptability of that risk. This culminates in a decision on whether to allow the requested action to proceed or not, or to delay decision-making.

Risk communication

Risk communication involves an ongoing and iterative exchange of information and opinions concerning risks related to the proposed action and risk perceptions among developers, risk assessors, policy and regulatory experts, affected communities, and the general public during the risk analysis process. Communication regarding any subsequent regulatory decision is also part of this component.

While the entry point is usually the RA phase, the process is iterative and components may flow in parallel or loop back to previous steps (Fig. 3.1).

Fig. 3.1. Example of an iterative risk analysis process*



*Adapted from Food and Agriculture Organization of the United Nations *(13)*.

Problem formulation enables a structured evaluation of the effect of the GMMs on the protection goals and identification of risks of greatest relevance within the limits of proposed use. In the case of GMO risk analyses, problem formulation begins with the particular protection goals that inform national laws and regulations affecting their oversight. Problem formulation provides an opportunity for broad stakeholder engagement. It is important during the problem formulation process to establish the problem domain such that it encapsulates all the essential elements of the problem, while also specifying assumptions made and any constraints identified.

For GMMs, hazard identification would include determining novel hazards of concern on a case-by-case basis for the particular genotype/phenotype being tested and the receiving environment with respect to a comparator (Section 3.4). This should include assessment endpoints, methodology and information on the GMMs (e.g., the modification they contain, the expression of the modified trait, their physiology, behaviour and ecosystem interactions in the receiving environment) in order to enable a structured evaluation of their potential effects on protection goals. Protection goals such as loss of biodiversity may be operationalized to include more specific goals, such as impacts on threatened species *(14)*. Attention, likewise, should be paid to plausible health hazards, especially given the intended use of GMMs for disease control. Problem formulation and hazard identification include consideration of potential exposure scenarios, each of which details a causal pathway identifying all the steps from the release of the GMMs to a specific harm. This process provides a systematic framework to organize existing knowledge, identify relevant new knowledge, and enable hypothesis testing *(3)*. As an example, problem formulation and hazard identification exercises conducted for GDMMs with low-threshold gene drive systems for prevention of malaria transmission in Africa identified concerns about biodiversity, human and animal health, and water quality *(15, 16)*.

Hazard identification is followed by the characterization of the likelihood (exposure assessment) and consequences (hazard characterization) of the identified hazards being realized as harms, based on available evidence such as laboratory or field data, information from the scientific literature, computer simulation modelling, and expert opinion. Risk characterization provides an overall estimation for each risk based on the evaluation of likelihood and consequences. An important concept in the RA process is that, although an event may be likely to occur, it may not be deemed harmful, in which case the risk could be judged as negligible. Some have suggested an integrated approach to RA that would include the participation of ethicists in addition to biosafety professionals *(17)*.

The risk report provided by the regulatory authority presents a composite view of all the risks and a recommendation of whether the risks are acceptable or need to be managed. Where possible, it also identifies strategies to mitigate or manage any risks that are deemed unacceptably high. It may be necessary to re-assess risk in the presence of any additional RM strategies that are introduced. RM of GMMs should be proportionate to a country's stated requirement to preserve its protection goals, such as those related to health, environment or biodiversity.

The limit of risks that are acceptable at any stage of testing for any outcome is a policy decision based on several criteria, including the range of potential impacts and the feasibility and expected effectiveness of RM processes. The overall risk of undertaking the action (testing or implementation of GMMs) may be considered by decision-makers in the context of relevant alternatives, such as the risk of no action or the risk posed by conventional control methods. Decision-making related to the implementation of GMM products as a public health tool will likely

consider other factors, such as benefits and costs (including RM measures and any unmanaged residual risks). A decision of no action or a delay in decision-making could feed back into a re-analysis of the proposed plans. This might, for example, entail a need to collect additional data or revise the study design and/or RM plan. After approval for the action has been obtained, it will be necessary to monitor the effectiveness of the RM measures, and results will feed back into the iterative cycle of RA.

Risk communication involves an interactive exchange of information and opinions throughout the risk analysis process *(18)*. At its best, it underpins RA and RM by enabling those with interests or concerns to provide input and make informed decisions about the acceptability of the use of GMMs in their area *(19, 20)*. Opportunities for dialogue with stakeholders should be provided in an ongoing and timely manner, with information communicated clearly and comprehensibly. Stakeholders should be included in the problem formulation and hazard identification steps in order to allow the problem space to be fully explored and defined. Stakeholders should also be involved in discussions of RM options. Risk communication has implications for and commonalities with community engagement and informed consent (Section 4). Effective risk communication requires sufficient knowledge of the stakeholder groups to enable development of appropriate communication tools; willingness to accept stakeholders as legitimate partners in the process and to value their opinions; credibility and transparency in communications; and the ability to convey a fair representation of potential risks and benefits (Section 4). Discussions are ongoing with regard to the appropriate role of socioeconomic considerations in biosafety decision-making. Some countries are incorporating requirements into their biotechnology regulatory procedures *(21, 22)* (Section 3.10).

3.2 Types of risk assessment

The release of GMMs raises different, but not entirely novel, issues to those previously addressed for GM plants. Arguably, the most important biological difference is the possibility of autonomous dispersal, although this has also been a consideration for other GMOs, e.g., *(23)*. The expected persistence of certain types of GDMMs in the environment will be addressed in exposure characterization. A considerable amount of literature is available to guide the RA of GMMs and GDMMs, e.g., *(2, 24–28)* (Section 5), along with examples of risk and environmental assessments *(29–33)*.

Both quantitative and qualitative RA techniques may be considered for GMMs. Both methods enable the tracing of cause–effect pathways. Quantitative frameworks enable the expression of risk as probability distributions of adverse outcomes, e.g., *(34–37)*. Thus, quantitative RA attempts to assign numeric values to enable statistical treatment of the likelihood of various adverse events and the assessment of the potential harm. Qualitative RA assigns categories of risk, sometimes with relative scores reflecting the range of outcomes. Definitions and uncertainties in qualitative RA can be expressed in scales that enable some approximate quantification (e.g., high, medium, low or negligible). Both quantitative and qualitative approaches can be strengthened by data and models based on field trials and environmental monitoring. For GDMMs, the National Academies of Science, Engineering and Medicine (NASEM) report recommends that quantitative ecological RA be used for estimating the probability of immediate and long-term outcomes and public health effects in order to inform decisions about gene drive research, policy and applications *(38)*.

The wider environmental RA and RM guidelines from the United Kingdom *(7)* referred to earlier give useful guidance on how to assess the credibility or uncertainty of evidence in risk analysis, as does the Australian GM risk framework *(9)*. As mentioned, considerations for biocontrol agents also provide useful context for the RA of GDMMs *(2, 39)*.

3.3 Site characteristics

Risk questions form the basis of RA for the development and testing of GMMs at a particular location. These questions inform the types of baseline information needed to support safety characterization. Ideally, appropriate outcome measures will be agreed upon by developers, regulators and risk assessors in order to ensure an initial baseline dataset, and eventually data and information to assure GMM safety upon testing. Understanding the endpoints and intended consequences of GMMs requires an understanding of the relevant aspects of local mosquito biology and ecology, including population data, to provide a basis for estimating the movement of GMMs and their genetic material *(40)*. Knowledge of certain characteristics of the receiving environment (i.e., the ecosystem and its constituent parts at the release and dispersal sites prior to the presence of GMMs) will also be important. Baseline studies provide an opportunity to conduct relevant purpose-designed ecological studies to obtain key information for the RA and provide a comparison for evaluating the ecological impact of field releases.

Types of baseline data needed might include: the distribution of principal vectors in the release area and changes in vector density across seasons; the location of mosquito larval sites and swarming sites; genotypes, biting behaviour, fertility, fecundity, lifespan and flight distance of the target wild type mosquitoes in the release area; presence of other species at the site; knowledge of active transmission (if any) of the target disease pathogen at the site and transmission dynamics of the target disease; and information on human habitation, climatic conditions and geographical characteristics (see also Section 2.2.1). The ability to achieve ecological/geographical isolation is a site consideration for initial field releases.

Certain practical issues pertaining to the field site may also be of importance for RM planning. This includes knowledge of existing surveillance and control systems for both vectors and disease, and plans to continue existing or introduce new vector control practices. Researchers should consider storing data and specimens (e.g., mosquitoes, target pathogens) collected during baseline studies to create a repository against which to measure any changes resulting from the field testing of GMMs.

3.4 Appropriate comparators

The choice of comparators will be essential in the RA of any hazards associated with the presence of the transgenic construct in the mosquito. In early Phase 1 testing, the ancestral laboratory line from which the GMM line was derived, or a subsequent generation of this line, is a logical comparator. A potential benefit of using this as a comparator is that genetic similarity can be maintained, enabling precise scrutiny of the molecular modification in terms of genetic and phenotypic viability and variability. A disadvantage of using ancestral laboratory lines exclusively as a comparator is that the loss of fitness due to long-term rearing in the laboratory may lead to a less precise characterization of the effect of the genetic modification compared to wild

populations. For field testing, it is expected that the transgenic construct will be introgressed into a genetic background relevant to the field site (Section 2.6.1). Unmodified field-derived strains with the same genetic background as the GMMs will thus become more appropriate comparators for RA in preparing for field studies, as such assessment will require understanding of the genetic background together with physiological and behavioural characteristics *(40)*. Defining clear points for comparison, for example, a specific phenotypic characteristic such as adult longevity, will ensure that the risk evaluation remains credible, proportionate and focused.

A range of other comparators at both the organismal and systems level may also be appropriate, depending on the assessment endpoint *(28)*. For example, conventional vector control systems using insecticides may be an appropriate comparator for assessing the potential harm to biodiversity caused by GMMs aimed at population suppression *(40)*. In some jurisdictions, RA will also consider the risks associated with no action, i.e., not testing the GMMs.

3.5 Hazard considerations

Hazard identification must be specific to the particular GMM system, the genetic construct integrated into it, the traits expressed by the integrated material, and the scope of use. Thus, while GMMs (including GDMMs) share certain characteristics that present common hazards, other hazards are likely to vary on a case-by-case basis for each GMM product, receiving environment, and phase of testing. Diversity of expertise and experience would be valuable for the hazard identification process. All hazards characterized should be prioritized from the perspective of causing potential harms that are directly related to the protection goals identified in problem formulation.

Description of use should include: the proposed or expected release rate; release site(s)/receiving environment; release frequency; and spatial distribution and expected persistence of the GMMs (e.g., based on modelling or supported by contained use data). Description of any other control measures that will be undertaken at the release site, such as suppression of unmodified local mosquito populations with insecticides, before or after GMM release will also support scoping and hazard identification, and, to some extent, inform risk mitigation measures and monitoring in a case-by-case manner.

The RA should thoroughly account for the molecular characterization and consider all hazards associated – from the generation of the transgenic construct to its genomic integration into the modified mosquito. Typically, molecular characterization of the transgenic construct and the sequences integrated in the GMMs determines whether the genetic sequences being introduced, their source/origin, method of generating the final transgenic construct, transformation event, site of integration in the genome, and integrated transgene copy number harbour any hazards that could lead to harms to the environment or human or animal health (Sections 3.5.1 and 3.5.2). Similarly, insertion site analysis aims at determining whether there are any position effects due to the insertion, such as into a known coding or regulatory sequence, or an increased chance of genomic instability such that the modification is lost or inactivated over time. These hazards are weighed in comparison to the parental background genotype of the GMMs.

Therefore, the parental background of the GMMs should be described, including the species and strain, geographical source, number of generations over which colonies have been maintained, and the extent of replenishment with wild stock. The methods used to generate the GMM lines and

sequences and schematic maps of the genetic construct are usually required. Original sources used for each individual sequence or element of the final transgenic construct, the source of donor genetic material, its size and intended function should be described. Core information on the actual sequences inserted (or deleted), the size and copy number of detectable transgenes, and their functional organization is necessary. Details should be provided on the developmental expression of the transgene (or modification through knockout deletion based on transgenic technologies) during the life cycle of the GMMs. It will be important to monitor the stability of the insertion and its expression over multiple generations in Phase 1 laboratory and population studies in order to determine whether the characterization of the GMMs is valid over time and to provide a basis for predicting their behaviour after release *(40)* (Section 2).

Phenotypic characterization builds on the molecular characterization, as it assesses the functional aspects of the integrated sequences at their site of integration in the particular GMM's genome. The GMM's physical/morphological (e.g., anatomical differences – mouthparts, wings, size, life span), behavioural (e.g., biting frequency, indoor or outdoor biting preference, flight distance), physiological attributes (e.g., different incubation period for the pathogen in the mosquito) can be investigated using suitable comparators (Section 3.4) to determine whether the expressed genetic modification has an impact on traits that could cause adverse events for human and animal health or the environment. The RA for GMMs should consider the stability and specificity of trait expression in relation to the intended effect of the transgenic material at the population level and the consequences of incomplete or partial transgene function. The characterization of stacked events should consider the stability of the inserts, expression of the events, and potential synergistic or antagonistic effects with regard to phenotypes rather than individual modifications. Hazards related to the GMM's phenotypic characteristics should be assessed with the receiving environment in mind, as this will account for any environmental, geographical and other pertinent conditions that could impact the severity or consequences of the identified adverse event, thereby affecting the overall risk.

Table 3.1. Safety considerations for GDMMs with low-threshold gene drive systems (adapted from *(41)*)

Health	Environment
• Increased abundance of the vector mosquito species • Alteration of the vector species that results in the increased ability to transmit one or more pathogens • Reduced capability to control the target species by conventional methods • Increased allergenicity or toxicity • Alteration of the target vector species that results in the increased virulence of one or more pathogens	• Spread of the transgenic construct to another species that results in harm to the wider ecosystem • Removal of the target vector species from a community resulting in harm to other species that directly depend on it for some essential service, such food or pollination • Removal or alteration of the target vector species producing a detrimental second-order effect, such as increase in a harmful competitor species • Removal or alteration of the target vector species causing harmful higher order effects that are amplified within the ecological community

Despite the need for case-by-case evaluation, it is possible to describe some of the more general potentialities that should be considered in RA. A hazard may arise either directly from the intended effect of a genetic modification or indirectly through an unintended deviation from that intended effect. Hazards associated with GDMMs are expected to be similar to those for other types of GMMs; however, the RA must take into account the possibility of higher levels of environmental exposure due to persistence and spread. General considerations for ensuring the safety of human and animal health and the environment have been described for GDMMs carrying low-threshold gene drive systems (Table 3.1). These broad considerations are derived from problem formulation discussions involving primarily technical, RA and regulatory experts *(15, 16)*, and take into account the risks identified by various civil society groups (Section 1).

3.5.1 Health hazards

The health hazards of GMMs (Table 3.1) are expected to be similar for both humans and animals *(15)*. Altered larval competition and/or accelerated maturation could lead to increased abundance of vector mosquitoes. Changes that could lead to increased abundance, such as increased fecundity, egg production and survival, can be assessed in physical confinement (Table 3.2). Nuisance biting could increase if female mosquito abundance increases substantially, since only females bite humans or animals. However, increased abundance must also be considered in the context of other hazards.

Biological alterations, such as those leading to increased female abundance, or increased blood feeding behaviour or vector competence relative to wild type populations, could affect disease transmission. Vector competence for the pathogen(s) of interest, and potentially for certain other pathogens known to be transmitted by the GMM species, can be assessed in the laboratory to ascertain whether there has been any unexpected increase in the potential for disease transmission *(40)*. During field testing, passive surveillance should be considered as a safety precaution to monitor for increased incidence of the target disease(s) or other mosquito-borne diseases known to occur in the area.

It would be undesirable for GDMMs to confer increased insecticide resistance on the targeted mosquito population. It is currently envisioned that GDMMs will be used to complement conventional vector control methods. The insecticide susceptibility of the GMMs can be measured in the laboratory *(42, 43)*.

Increased allergenicity or toxicity of GMMs has been proposed as a speculative risk to humans, although no supporting information is available. While ingestion has been suggested as a possible route of exposure, this is likely to be quite rare and thus unlikely to pose a significant hazard *(15)*. The most likely route of exposure to GMMs is via biting and blood feeding. The saliva of all mosquitoes naturally stimulates an immunological response in most persons and a strong allergic response in some *(44)*. There is considerable cross-sensitivity to the salivary proteins from wild populations of mosquitoes. Therefore, it would be difficult to attribute a GMM-specific causal effect in the context of such natural variability. However, with GMM technologies in which female mosquitoes will be released or transgenes will be expressed by female progeny, it will be appropriate for the RA to consider whether a transgene product is expressed in the saliva and, if so, whether this protein is significantly similar to a recognized allergen (for example, using Codex Alimentarius guidance for testing the allergenicity of GM foods) *(45)*. In such a case, further studies

may be warranted, and established validated protocols for assessing the allergenicity of proteins, as through dermal exposure, could be followed. The potential for the toxicity of water-borne GMM larval stages to cause harm to individuals or aquaculture has been raised as a concern *(16)*. Similarly, established methods for testing the toxicity of GM foods can be adapted to GMMs *(45)*. In this regard, the toxicity of commonly used larvicides may be a valid comparator.

The possibility that the target pathogen could develop resistance to the effector mechanism has been raised as a hazard for GDMMs aiming at population replacement, thereby resulting in reduced GDMM efficacy *(46)* (Section 2.3.4). This possibility should be weighed against the potential benefit during the period when the intervention is efficacious. However, an additional aspect is the potential for the alteration to result in increased pathogen virulence. Current science indicates that the best defense against the selection of resistant pathogens is to incorporate multiple effector systems in the GDMMs.

3.5.2 Hazards to the environment

Some GMM interactions with other organisms in the environment may result in hazards being actualized to harms to the receiving environment. Different GMM strategies will be associated with different prospective ecological interactions. For example, population suppression strategies are expected to persist in the environment for a limited time due to the resulting reduction in overall numbers of the target species. GDMMs aimed at population replacement, however, will remain effective only as long as they are present at high levels in the environment.

One possible ecosystem interaction might arise from the transfer of genetic material from the GMMs to other species. Vertical transmission may occur as a result of productive mating with related species. This could be desirable if those species are also known disease vectors, as in the case of the *Anopheles gambiae* species complex. Mating barriers are expected to prevent vertical transmission to more distant species. The transfer of stable genetic material from one organism to another non-target organism (NTO) without reproduction is called horizontal transfer (HT). The possibility that HT might occur directly to an NTO or be facilitated by an intermediary microorganism should be considered. Most GMOs tested and used commercially to date have been plants, and this prior use history provides data for inquiries into the occurrence of HT. No evidence of HT from GM plants to microorganisms has been detected in the field over decades of observation and millions of hectares of planting *(47)*. This suggests that the occurrence of HT from the relatively less abundant GMMs is likely to be extremely rare. A prior problem formulation exercise focusing on GDMMs with low-threshold gene drive systems concluded that HT is unlikely to occur during a relevant time scale and is not a pertinent pathway to harm *(15)*. However, some have expressed concern that the characteristics of certain types of GDMMs may increase the risk of HT due, for example, to the properties of the gene drive construct *(48)* or to prolonged exposure to the environment.

While questions of likelihood are one component of RA, the other component – the consequences or resulting harm – must also be considered. Therefore, it is important to ask about the extent of harm that might be caused by the transfer of genetic material via vertical transmission or HT. A relevant consideration is the known function of the transgenic construct and whether that function can be preserved in the NTO. For example, do the transgenes contain components that could plausibly confer a selective advantage to the intermediary microorganism *(49)*?

Another possible ecosystem interaction involves the potential negative effect of removing a target species that directly provides an important ecosystem service or an NTO that provides such a service. With regard to RA for population suppression strategies, it should be noted that the removal of mosquitoes and other insect disease vectors using conventional control methods has historically been judged to be desirable from a public health perspective; the ecosystem effects of species removal have not been considered an issue in the RA for these methods. Literature review can be informative. For example, a review of evidence for the negative effects of decreased *An. gambiae* density on potential NTO predator species found no evidence to suggest it is a critical food source *(50)*. If a plausible pathway to harm due to removal of the target species or a secondary species has been identified and there is a need for experimental evidence, population-level microcosm or mesocosm studies could help to evaluate the specific effects of the GMMs on selected NTOs, e.g., *(51)*.

The choice of appropriate NTOs for studies of ecosystem interactions is a complex decision that should be prioritized based on the results from the problem formulation step and the protection goals. Assessment endpoints deriving from the operationalization of the national protection goals will assist with NTO determination for the RA on a case-by-case basis. Existing guidance, such as that from the European Food Safety Authority (EFSA) *(52)*, could provide examples for the choice of NTO in the environmental RA of GMMs. Possible categories might include natural enemies, competitors, pollinators, species of conservation, cultural or food chain value, decomposers and host animals if they are appropriate to the scope of the particular RA. Additionally, it may be useful to adopt the hierarchical methods utilized in safety testing for conventional biocontrol agents to identify other species most "at risk" based on likely interaction *(53)*. For GDMMs, it will be informative to examine the genome of the identified NTOs for presence of the target site of the gene drive element *(40)*.

Problem formulation conducted for GMM population suppression strategies has identified the concern that a resulting empty ecological niche may be filled by alternative unwanted species. For example, studies of competitive interactions between (unmodified) *Aedes aegypti* and *Aedes albopictus* demonstrate that *Aedes albopictus* larvae are superior competitors for resources than *Aedes aegypti* over much of their range *(54, 55)*. This has implications for the invasion and establishment of *Aedes albopictus* after *Aedes aegypti* is suppressed to inhibit transmission of dengue and other arboviruses, contributing to concerns over other mosquito species. Available information from laboratory and field studies will help to assess the likelihood and the ecological or health consequences of the empty niche hazard. For instance, in the case cited, available evidence indicates that *Aedes albopictus* plays a minor role in dengue transmission due in part to different host preferences and reduced vector competence *(56, 57)*. The potential for higher order ecosystem effects would be most plausible if the GMMs were targeting a known keystone species.

Data on preliminary ecological or behavioural patterns associated with the modification, obtained through longitudinal, population-level cage trials of both GMMs and unmodified comparators, would be useful to enable assessment of the risks posed by such ecosystem interactions. The use of semi-artificial microcosm and mesocosm systems *(58)* that aim to mimic the key aspects of the receiving environment would enable more accurate characterization of the GMMs' population dynamics and population-level characteristics than simple laboratory population cage studies. While not considered essential (Section 2), studies in larger caged environments provide the potential for interactions with a limited range of ecological complexity, offering a bridge to more

comprehensive physically and/or ecologically confined field trials. Careful choice of experimental design and planning might enable a range of potential ecological characterizations, such as:

- the role of density dependence in the population dynamics of the target species (Section 2.3.3); the timing of density-driven events that affect survival, development rate and/or fecundity can be explored using population cage and semi-artificial microcosm and mesocosm trials, appropriate statistical analysis and mathematical modelling;
- comparison of discrete dynamics (e.g., seasonal factors such as rainfall) and continuous dynamics (e.g., competition for host finding) under semi-artificial conditions;
- effects of release numbers/schemes, or invasion potential of GDMMs.

While many GMM characteristics that are useful for safety determination can be measured in containment, continued monitoring for adverse effects on health or the environment must be included in subsequent phases of testing (Section 3.8).

3.6 Utility of mathematical modelling for risk assessment

Modelling as a predictive tool that can be iteratively tested and enhanced using data obtained in Phase 1 and field studies will play a major role in bounding the risk of adverse events related to the spread and dispersal of GMMs, especially GDMMs. Modelling results will be particularly critical for new product classes where prior use information is not available *(59)*. Computer simulation modelling can highlight the range of parameters necessary for RA, which will aid in planning for data collection in both confined and field testing. The overall aim of modelling in the RA context is to predict behaviour based on the properties and assumptions of the transgenic modification that may be helpful in assessing the likelihood of events (Box 3.2). The more closely the model captures the genetic, demographic and ecological complexity inherent in the study, the more accurate the prediction is expected to be.

Given a specific set of genetic modifications, computational models might be used to predict whether or not the fitness of the GMMs will be enhanced by the genetic modification. Modelling of inter-specific interactions over time could also be useful to reveal potential structural alterations to the ecological (biotic) effects. In this regard, the collection of ecological data from the proposed release site should be a priority for baseline field studies; data from small-scale semi-artificial population trials in Phase 1 could also be informative. Data collected from small- and large-scale field testing can be used in computational models in order to develop sampling schemes to identify any occurrences in the course of implementation with substantial potential effects on disease. Modelling may also provide insights into the effectiveness of proposed remediation strategies, e.g., *(60)*.

Box 3.2. Modelling to underpin risk assessment

Modelling can support RA by helping to predict GMM behaviour under field conditions. For example:

Altered fitness

In an experimental system where GMMs containing a particular anti-pathogen effector gene were continually fed on mice with a high level of parasites, increased fitness of the malaria-resistant mosquitoes was reported *(61, 62)*. Given such an observation, modelling might be used to determine the implications of the fitness effect for spread of the transgenic construct, abundance of the vector mosquitoes and malaria transmission, e.g., *(63)*.

Spread and dispersal

Modelling can provide a basis for predicting the spread of gene drive systems in wild mosquito populations. For example, a population genetic model was used to simulate the behaviour of different gene drive systems intended to be localizing; the model provided insights into the potential for spread of the genetic element within the population into which it is released and dispersal to neighbouring populations *(64)*. Spatially explicit models can be used to understand the influence of seasonality and geography on the spread of GMMs modified with gene drive systems *(65)*.

Resistance

Modelling can be used to estimate how rapidly resistance to gene drive systems will develop and thus limit their utility. Examples include prediction of the duration of protection over different dispersal distances for a population replacement approach *(66)* and likely accumulation of resistant mutations for a population suppression approach *(67)*.

3.7 Target safety profile

As development moves from Phase 1 confined testing to field testing and implementation, the scope and assessment endpoints for RA will evolve. However, as for other public health products, the target product profile for GMMs is expected to include some overall safety, and efficacy, goals for the minimum essential and ideal products *(68, 69)*. Harm can be considered in comparison to a reference outcome. For example, in the RA for a modified mosquito product in Australia, the question of whether it "causes more harm" than populations of wild mosquitoes managed under current practice has been used as a benchmark for the acceptable limit of safety *(35, 70)*.

In the case of GDMMs containing low-threshold drive systems, the decision to move an investigational product from physical confinement (Phase 1) to field testing may be informed by the standards and practices established for biological control agents, for which the potential for irreversibility and dispersal to areas beyond the release site has been recognized (reviewed in *(39)*). A suggested safety criterion for moving to field testing *(41)* is a well-reasoned justification that the GDMMs will do no more harm to human health than wild mosquitoes of the same genetic background and no more harm to the ecosystem than other conventional vector control interventions.

3.8 Risk assessment and management at different testing phases

As noted above, given the various potential hazards that might be encountered, RA and related RM must be developed on a case-by-case basis, focusing on the particular GMM system, receiving environment, and objectives within the phase of testing under evaluation. For example, the level of exposure for humans, animals and the environment is expected to be less in confined trials compared to open releases, with sterile GMMs compared to those with gene drive, and with self-sustaining population suppression compared to population replacement strategies. RA should consider whether some of the precautions detailed below for self-sustaining, non-localizing GDMMs also are pertinent to localizing or self-limiting GMM systems.

At each level of testing, from laboratory through field trials, the aim of specific RA and any resulting RM approaches will be to ensure that there is an acceptable level of safety and to improve understanding of the potential risks associated with the eventual deployment of the GMMs. The views of regulatory bodies and institutional oversight committees (Section 5) will help to determine what safety information is required, what endpoints will be monitored, for how long monitoring should continue, and for how long the capacity to manage any adverse effects must be maintained. Monitoring may need to continue for some period of time after collecting the necessary efficacy data in order to examine the possibility of longer term safety effects.

It is likely that regulatory authorities will ask for a mitigation or remediation plan as a component of RM. These plans must be tailored to the characteristics of the GMMs, the intended use, and the perceived harm. Such a plan may, for example, involve expanded application of conventional vector control tools or release of mosquitoes carrying a resistant allele intended to restore function *(41)*. If the plan involves the development of a new technology, such as proposed reversal or recall systems for GDMMs, e.g., *(71–73)*, those systems must be developed alongside the GMMs whose effects they are intended to mitigate or remediate, and under the same oversight mechanisms, so that they will be ready for use if needed. Trial insurance will be an important consideration.

At each testing phase, the process will involve RA for the phase about to begin, including implementation of RM indicated during that phase, followed by data collection to inform the RA for the next phase. Monitoring plans are considered to be a component of RM, although the conduct and analysis of monitoring results will be part of study conduct and data collection. Each study must be designed to obtain key information to decrease uncertainties in the RA and support decision-making for the subsequent level of testing. RA should include concerns expressed by the local community where the tests will be conducted. Upon obtaining the appropriate regulatory, ethical and community approvals (Sections 4 and 5), the trial will be conducted with the agreed-upon RM processes in place.

The transition from each phase of testing to the next should involve retrospectively evaluating the RA and RM that was put in place at the beginning of the phase and determining whether the performance characteristics that were measured warrant progressing to the next phase of testing. This determination should be based on previously established efficacy and safety endpoints. Any previously unforeseen hazards noted during the study should be factored into the RA and RM for the subsequent phase and considered in the decision on whether to progress. The decision to move forward with further testing will require approval from the appropriate oversight and regulatory bodies, as well as appropriate community understanding and agreement (Section 4).

3.8.1 Phase 1 – Laboratory and population cage studies

The purpose of Phase 1 testing is to gather initial safety and efficacy data to enable decision-makers to determine the feasibility of moving to Phase 2. This early testing phase focuses primarily on the biology of the GMMs and integrates molecular, genotypic, phenotypic, behavioural and population-level characteristics. The data collected at this phase will expose differences between the GMMs and the comparator mosquitoes that should be assessed for their potential to cause harm.

Risk assessment

Phase 1 testing will be conducted in a laboratory, insectary or indoor population cage under physically confined, or contained, conditions. Because this is an early stage of development, there will inevitably be limited information on the stability and effect of the genetic modification. A cautious approach is warranted, primarily due to uncertainty rather than to any established hazard. RA in preparation for Phase 1 will determine the conditions under which laboratory studies can be conducted, including the acceptable level of exposure to GMMs by research personnel, acceptable security measures to prevent GMMs from escaping, and appropriate methods for disposing of waste materials. RA should consider the phenotype of the GMMs, their potential to survive and become established in the receiving environment, and, when the target species is present in the environment, the potential for the transgenic construct to spread within the local population.

Risk management

The adherence of all staff to SOPs for safety will be a fundamental component of RM in Phase 1, and will require advanced training and practice. An SOP is a written plan describing the procedures to be carried out during the evaluation of GMMs. RM measures for environmental impact will include containment of live mosquitoes and destruction of dead mosquitoes and waste materials as appropriate to their hazard level *(74)*. RM measures for human health will include ensuring that GMM colonies and feed sources are free of human pathogens; ensuring that laboratory staff are not carrying mosquito transmissible diseases; and limiting unintended biting opportunities by preventing and removing mosquitoes flying outside cages and ensuring that laboratory staff wear suitable protective clothing. For Phase 1 studies conducted in regions hospitable to the GMM species, RM to respond to escapes from the laboratory might include escape detection systems, standby capacity sufficient to control adults within the accessible range, and/or conduct of experiments in seasons when adult dispersion and mosquito breeding sites will be limited. Where testing of vector competence or infection cycles in GMMs is undertaken, particular care should be taken to ensure the safety of laboratory staff. All of the above build upon standard precautions and are also good practices in rearing fertile non-GM mosquitoes, particularly when they are being handled in areas where they are exotic and could establish following escape.

Appropriate containment in Phase 1 testing will be determined by RA. Additional containment considerations have been recommended when studies are conducted in areas suitable for establishment of the GMMs and the GMMs are modified with transgenic constructs capable of spreading in the local population of the target species *(41, 75–77)*. Building on widely accepted arthropod containment guidelines *(74)*, the appropriate level of containment for such GDMMs has been characterized as “enhanced” Arthropod Containment Level (ACL) 2 conditions *(77)*. Briefly, these include triple-nested barrier containment as suitable for mosquitoes (but not the

microbe-specific measures of ACL3 if the GDMMs are uninfected). Precautions to be taken in the maintenance of these GDMMs include the use of visible markers and/or PCR methods to detect the transgenic construct, regular authentication of all strains held in the facility to test for contamination with the transgenic construct, and thorough inspection of all mosquito shipments from the facility.

Table 3.2. Example parameters that may be tested in laboratory studies to inform the RA for GMMs[a]

Parameters	Example hazards	Assessment methods	Assessment endpoints
Female fecundity **Oviposition rate**	Increased vector abundance	Cohort experiment; life table analysis	Is it limited by population density and/or individual physiology? Is there a significant difference versus the unmodified comparator?
Egg development rate **Larval development rate** **Pupal development rate**	Increased growth potential; reduced predation	Cohort experiment; life table analysis	Is there a significant difference versus the unmodified comparator?
Egg survival **Larval survival** **Pupal survival**	Increased vector abundance	Cohort experiment; life table analysis; population-level modelling	Is the parameter density-dependent? Is it under-/over-compensatory? Does it differ significantly?
Adult emergence	Increased vector abundance	Cohort experiment; life table analysis	Does the timing of adult emergence differ significantly?
Adult size	Increased vector fitness	Cohort experiment; life table analysis	Is adult size significantly different?
Adult survival	Increased vector activity; more effective mating potential; increased biting efficiency for females	Cohort experiment; life table analysis; population-level modelling	Is it density-dependent? Is it significantly enhanced/diminished by the modification?
Mating strategy	Increased vector abundance; separation of GM and wild types	Cohort experiment	Is there assortative mating? Are there costs to male/female gametes? Does the modification affect mating competitiveness?
Sex ratio	Increased female abundance; increased biting potential if more females	Cohort experiment; life table analysis	Is the sex ratio substantially different from the null expectation of Mendelian inheritance patterns?
Flight ability	Increased vector activity; more effective mating potential; increased biting efficiency for females	Cohort experiment; physiological experiment	Is flight duration or distance significantly different?

Parameters	Example hazards	Assessment methods	Assessment endpoints
Biting rate	Increased disease transmission	Cohort experiment; physiological experiment	Does the biting rate differ significantly?
Vector competence[b]	Increased disease transmission	Cohort experiment; physiological experiment	Is the capacity to harbour pathogens significantly enhanced/diminished?
Insecticide resistance	Increased vector abundance	Standard insecticide dose response testing procedures	Is it expected to alter the competitive status of transgenic lines significantly? Does it make transgenic lines significantly less amenable to conventional control?

[a] The RA should focus on the hazards (changes that may lead to harm as a result of the genetic modification), the experimental methods to measure these and the exposure assessment. Most relevant characteristics should be assessed, as determined on a case-by-case basis according to the type of GMM. References to 'differences' mean differences between the transgenic strain being tested and the appropriate comparator.

[b] Increased ability to vector the pathogen of interest, as well as selected other pathogens known to be vectored by the targeted mosquito species. In most cases, this can be measured using membrane-feeding assays, e.g., *(78, 79)*.

Study conduct and data collection

Safety data relevant to the potential for increased disease transmission can be collected at this phase, including any changes in fitness parameters, vector competence, behaviour or insecticide susceptibility. Data on allergenicity, toxicity, and genotypic and phenotypic stability will also support safety assessment. Studies on the potential for off-target effects and for evolution or selection of resistance mutations at this phase will be particularly important for GDMMs employing endonuclease-based systems *(40)*. Alterations to target populations through changes in the demographic size and structure or changes in behaviour may have an impact on the wider environment and/or human health. Experiments to determine whether these alterations might lead to any of the specific harms identified in problem formulation can begin to be addressed at this stage.

Examples of Phase 1 studies that may be undertaken to characterize the biology of the GMMs are detailed in Table 3.2, with unmodified mosquitoes of the same genetic background serving as the comparator in most cases. The most relevant characteristics should be prioritized on a case-by-case basis, according to the type of GMMs. The results of Phase 1 testing will provide a basis for determining whether safety data are sufficient to support the decision on whether the GMMs may proceed to Phase 2 field release or whether physical confinement under semi-field conditions should be considered as an intermediate step to obtain additional safety information.

The needs for Phase 1 safety studies of self-sustaining, non-localizing GDMMs have been considered in further detail *(40, 41)*. At this phase, considerations for safety to the environment have much in common with the RA for biocontrol agents, which are also expected to spread and persist in the environment and whose releases may be difficult to reverse. In particular, the concerns about niche replacement and effects on NTOs are shared for both biocontrol agents and GDMMs. For these GDMMs, safety evaluation at the end of Phase 1 will form a critical decision point for whether to enter into any stage of field testing (Section 3.7). Therefore, particular emphasis will be placed on collecting data in Phase 1 that will reduce specific uncertainties about safety in the next level of RA *(40, 41)*.

3.8.2 Phase 2 – Confined field studies

Phase 2 studies are intended to enable GMM testing in a more natural setting than the indoor studies in Phase 1, while still limiting environmental exposure. The goal is to collect data related to the GMMs' biology and behaviour in a confined environment that includes natural features such as climate, native flora and alternative hosts. These data should more closely reflect the GMMs' natural performance, including how the construct functions in the local genetic background at a larger scale and how it interacts with existing control methods. This knowledge will inform study design and provide safety data to support the RA for Phase 3.

Risk assessment

RA will take into consideration the level of confinement proposed in Phase 2. Confinement could be molecular (Section 1), physical (outdoor cages), ecological/geographical (e.g., surrounded by inadequate breeding sites or by barriers to mosquito migration such as water, deserts or mountains), or some combination of these measures.

Understanding the limitations of confinement measures and the consequences of a breach of confinement is fundamental to RA at this phase. A breach of confinement may lead to the dispersal of GMMs or of genetic material into the wider receiving environment. Dispersal of transgenes into the environment is a greater possibility with GDMMs. Breaches of physical confinement from an outdoor cage facility might be the result of natural disasters, structural failures, human error/accidents, or deliberate actions. The RA should take into account cage designs, experimental planning, emergency preparation, training and site security *(24)*.

RA should consider whether there is a mechanism available for practical and reliable monitoring of GMMs, as this will influence RM planning. Where release of male-only GMMs is part of the study design, the reliability of sex-selection methods prior to release should be considered. In preparation for Phase 2 testing, other biological considerations for RA should include what is known about the local dispersal and gene flow patterns of target mosquitoes and what pathogens they transmit in the receiving environment *(24)*. Reliable entomological, epidemiological and ecological data from the prospective field site is crucial for RA at this phase *(40, 41, 80)*.

For some GMM systems, RA may indicate that physical confinement/semi-field testing is not a necessary step in the testing pathway and that conditions of biological or ecological confinement allow for sufficient risk reduction. Previous evidence from laboratory studies or prior releases in other areas may demonstrate that the phenotypic properties of the GMMs and success of protocols to discriminate the sex of the released mosquitoes are sufficient to ensure a high probability of safety. For example, physical confinement may be less important in cases where Phase 1 results have demonstrated that there is limited potential for dispersal, such as for localizing GMM systems wherein the progeny do not mature to adults, or when the GMMs have low intrinsic fitness in the wild and are not expected to persist. A regional standard in North America accepts biological confinement for sterile transgenic arthropods, provided there are data on the efficacy of sterility *(81)*. It is important to note, however, that regulatory requirements will likely differ for physically confined and ecologically confined studies. This may also influence the decision on whether to conduct semi-field testing.

For self-sustaining, non-localizing GDMMs carrying low-threshold gene drive systems, in regions where there is a possibility that establishment could result from the unintended release from confinement of a small number of individuals, there would be a conflict between ensuring biosecurity conditions extensive enough to guarantee physical confinement and conducting semi-field testing to obtain data in a more natural setting. Semi-field testing, therefore, has not been considered to be a required step in the development pathway in this case *(41)*. However, regulators, communities and/or the public may view semi-field testing as an important component of incremental safety testing. If undertaken for these GDMMs, it would be best to couple semi-field and small-scale field release permissions in the context of regulatory applications due to the possibility of unintended low-level release from physical confinement. Ecological confinement likewise cannot be guaranteed for GDMMs carrying low-threshold gene drive systems in initial small-scale field releases. Geographical isolation is nevertheless recommended for the first field release to minimize the possibility of outward migration *(41)*.

Before moving self-sustaining, non-localizing GDMMs to outdoor caged testing or geographically isolated releases, a third-party all-hazards RA is advised to manage operational risks. Such an external and unbiased RA can help the developer to determine significant risks and identify those that require RM. Making this RA publicly available could also enhance public confidence in the research. This external RA will be separate from the RA conducted by regulatory agencies in support of a decision on an application to conduct work with GDMMs. Because of the possibility of release into the environment, RA for Phase 2 should consider potential adverse effects on NTOs or ecosystem services (Section 3.5.2). The risk of adverse effects at this phase would then be influenced by the level of exposure to the environment given the confinement measures imposed. Evidence to address uncertainties in the RA can be drawn from Phase 1 studies, modelling, scientific literature, and expert opinion. In some cases, developers of self-sustaining, non-localizing GDMMs may wish to consider the utility of prior field testing of a related self-limiting GMM strain as an intermediate step in order to obtain information to reduce uncertainties in the RA.

Risk management

In semi-field or ecologically/geographically confined field studies, the potential risks of GMMs to health and the environment are different and sometimes greater than those for studies in Phase 1. RM will emphasize decreasing the potential harms associated with escape/unplanned release of GMMs through breaches. It is anticipated that the nature of potential risks will be related to the anticipated persistence and dispersal of GMMs in the environment. Factors such as density dependence, mosquito population size and age structure affect the design of measures to mitigate risk. Considerations for cage design (in the case of semi-field tests) and ecological/geographical location will influence potential for dispersal.

Aspects of local geological and ecological conditions, as well as regulatory criteria will underpin the design of field cages and trial implementation *(82, 83)*. Further simple RM measures, including restricted access, clear and well-managed SOPs, and appropriate engagement considerations (Section 4) could all mitigate hazards associated with confined trials. While clear research protocols will be necessary beginning in Phase 1, SOPs will become increasingly important as testing moves forward. SOPs should describe the lines of responsibility and the RM strategies and options for the study. Staff training and auditing for compliance with such procedures will be a priority in preparing for confined field testing. For example, SOPs for semi-field testing could describe the expectations

for record-keeping and other quality assurance processes; document how transgenic material should be moved from the laboratory to the field site; provide protocols for ensuring site security and cage suitability; detail procedures for monitoring for unintended releases during the trial and responding to detection of escapees; and describe the post-study removal of material and cages *(24)*. Monitoring the performance of containment measures, such as physical integrity of screens and the operation of entryways, and adherence to SOPs will minimize risk from unintended release. Where practical, advance measures should be taken to limit the establishment of GMMs within the potential dispersal zones around the cage, such as controlling wild mosquitoes and limiting available larval breeding sites. Because the cages in semi-field tests will be outdoors, SOPs should also be established for responding to unexpected events, such as acts of nature, that might compromise containment. The need for security measures to prevent human or animal intrusions should be thoroughly considered.

Plans for mitigation or remediation actions required in the event of accidental release should be agreed upon in advance with regulators and the community. For physically confined studies of self-sustaining, non-localizing GDMMs, if the field cage is not located in the planned site of small-scale release and/or there has been no approval for release, researchers should have a strategy for monitoring the persistence and establishment of the GM trait in the wild mosquito population, along with any mitigation or remediation activities, developed in agreement with regulators. Because it is expected that safety will already have been assessed carefully in laboratory testing, remediation may not be an immediate concern if low-level escapes are detected. However, ongoing monitoring of the target mosquito population, along with some predetermined process for safety monitoring for any unintended effects, will likely be a regulatory requirement.

Depending on the characteristics of the mosquito species and the drive, ecological/geographical confinement may not be complete for GDMMs. However, it is possible to select initial release sites where ecological and geographical conditions minimize the possibility of the outward migration of GDMMs and inward migration of wild type mosquitoes, which should simplify monitoring *(41)*. Islands may provide geographical isolation, but the monitoring plan must still consider means of human transportation that could provide a route for escape. For initial release at a mainland site, monitoring around the fringes of the site is a possible strategy. However, the geographical area involved could be large and sampling at the fringes could be resource-intensive. As in the case of islands, any means of human transportation into and out of the release site must be taken into consideration. Other possible methods for long-range dispersal should also be considered in the monitoring plan *(84, 85)*. Developing the capability to detect broader dispersal of GDMMs will be an RM issue.

Although it is not expected that impact on infection incidence will be detectable in small isolated releases in Phase 2, passive surveillance through local health care facilities may be considered as a safety precaution to monitor for increased transmission of mosquito-borne diseases. If disease monitoring is included in RM, it will be crucial to be able to distinguish between increases in the transmission of mosquito-borne diseases due to GMM release and increases due to other causes. At this stage, the design of monitoring methods may require the involvement of clinical researchers and ecologists in order to ensure that a suitable signal-to-noise ratio is achieved to protect from human health and environmental harms.

Study conduct and data analysis

Phase 2 enables evidence on GMM performance to be gathered under more natural conditions. This evidence will inform a more robust RA and RM plan for open field trials in Phase 3. However, confinement in Phase 2 studies introduces differences from the natural environment that may affect the performance of the GMMs and their interactions with other organisms in the study. Consequently, it will be important to prioritize the most relevant information needed to make decisions about moving forward. Because the environment has a higher degree of influence on these studies, and the ability to control levels of exposure to some environmental stressors is more limited, it is critical to ensure that studies are sufficiently powered in order to generate data that enable reliable conclusions.

Identification of clear endpoints for the Phase 2 field evaluation will enable the operationalization of protection goals, while basic ecological, entomological and epidemiological information collected during baseline studies at the field site will support comparative determination of the impacts of GMM release. Mosquito sample collection at the site and genome sequencing can provide insights into the target species' local population size, structure and movement. This information will be important for planning subsequent trials and for understanding hybridization with other local mosquito species. The relevant biological information to be collected and the period for monitoring will differ according to the GMM system and expectations for spread and persistence of the genetic construct, as informed by modelling. Suggestions for Phase 2 testing of GDMMs have been detailed *(24, 41)*. These include ongoing assessment of functionality according to the population suppression or replacement phenotype, and periodic sampling of the GMM population to determine the stability of the transgene and to detect changes in the genetics of the target mosquito population that suggest the possibility of a negative impact of the technology, as identified by RA.

Phase 2 studies should be structured to provide relevant information on the ecological processes critical to the evaluation of the GMMs in subsequent trials. Ecologists should be involved in the design and interpretation of studies beginning in Phase 2. Due diligence in this phase might involve observation of the GMMs' key interactions with mosquitoes of other species. Interactions with a few representative "sentinel" NTOs at the study site could be observed to identify and characterize any unexpected environmental effects (Section 3.5.2). However, assessment of ecological effects in this and subsequent phases must keep in mind that GMMs will most likely be implemented in conjunction with commonly used insecticide-based vector control methods that could have an independent effect on the ecosystem. Additionally, the complex relationship between mosquitoes, climate conditions and human behaviour may make it particularly difficult to attribute any observed ecosystem changes directly and solely to exposure to the GMMs.

Such complexity will likewise affect the causal attribution of changes in human health to the release of GMMs (Section 3.5.1). If a decision is made to monitor health effects at the trial site, care must be taken to collect information on other conditions that could affect this measurement, such as increased rainfall that would affect mosquito abundance. Comparison to a control area with similar demographic and climatic conditions is advised. Direct evidence of adverse impact on human health would provide rationale for stopping further releases and initiating mitigation procedures. In this regard, researchers are encouraged to consider the utility of a small DSMB with the appropriate expertise (Section 2.2.3), even at this early stage, to provide independent oversight of safety data and avoid biased decision-making.

3.8.3 Phase 3 – Staged open field releases

Phase 3 studies are designed to build on Phase 2 by increasing GMM access to the environment, while continuing to gather safety and efficacy data under real-world entomological, ecological and disease transmission conditions. Data from these studies will inform the determination of entomological and epidemiological efficacy, and, for GDMMs, support enhanced understanding of dispersal over time and space, activity of the modified trait and ecological interactions. Phase 3 releases should be designed to provide safety data that will be factored into decisions about the broad-scale implementation of the GMMs.

Risk assessment

Early small-scale releases will allow for observation of safety under different conditions, including different ecological and disease transmission conditions and/or different release designs. The RA for open releases will build incrementally on the RA for Phase 2 field studies, taking into consideration the location and characteristics of the release site(s), size of release (i.e., number of mosquitoes and geographical scale), duration of release, structure and knowledge of the vector population, local disease transmission dynamics, and any additional concerns expressed by the communities in which the tests are to be conducted. When selecting the site, RA could make use of geographical surveys (e.g., Global Positioning System [GPS], geographical information systems and high-resolution satellite images) and predictive models of habitat suitability, which could provide insights into mosquito ecology and dispersal potential *(86, 87)* and disease burden *(88, 89)*.

It is strongly recommended that the all-hazards RA be updated before moving to large-scale releases. When large-scale trials are focused on human disease control endpoints, aspects of human safety should be incorporated into the RA, including appropriate knowledge of the size of the human population, level of disease burden and ethical issues related to the testing of disease interventions (Section 4).

The spatial scale of a proposed field trial may have environmental consequences for established biodiversity protection goals. Therefore, RA should consider the spatial pattern and scale of the entomological/ecological risk *(90)*. Determining the appropriate scale for a release strategy requires an appreciation of the relationship between ecological processes, demographic processes and spatial aspects *(91)*. Because the effects of GMMs may extend to neighbouring areas if migration between populations occurs *(92)*, knowledge of the connectivity between the population within the target zone and the surrounding populations will be important for RA. For GDMMs, large-scale releases for testing epidemiological efficacy may constitute the first stage of regional deployment, and this possibility must be considered in RA.

Because GMMs are area-wide interventions with the potential for autonomous movement, and it is possible that more than one investigational product may be tested within the same general region, it will be important to be aware of not only conventional vector control tools being applied at the testing site, but also other current or prior releases of GMMs or other GM control tools, e.g., *(93, 94)*, in the surrounding area. This could complicate the RA and instigate a need for additional RM considerations.

Risk management

As testing moves to larger and more prolonged releases, quality control in production becomes an increasingly important issue. For some mosquito species, notably *Anopheles gambiae*, cryopreservation is not yet possible; therefore, GMM lines must be maintained through continuous breeding. Thought must be given to requirements for colony maintenance and ongoing monitoring for GMM fitness and genotypic and phenotypic functionality. Larger scale releases may involve transporting GMMs over some distance. Staff working at field testing sites should be trained on the risks of moving living specimens and should observe transport protocols when moving any material. SOPs should be put in place to ensure product quality in manufacturing, transport, and all along the "supply chain" from the facility to the point of release. These SOPs may be informed by examples from other large insect release programmes *(95)*.

RM in Phase 3 will be similar to RM in Phase 2, but will need to be expanded in scale to account for the lack of confinement and larger scope of intended release. Monitoring should be considered at four levels: for the presence of the released GMMs; for the presence of the transgenic construct in the local population of the target mosquito species; for health effects; and for environmental effects. Monitoring of GDMMs will likely require more resources than GMMs without gene drives, based on the potential for the transgenic construct to persist and spread.

Monitoring for the presence of GMMs will require resources for appropriate trapping and collection protocols, as well as facilities and resources for processing and analysing samples. GMMs should carry markers that easily distinguish them from non-transgenic mosquitoes and other GMMs. It will be important to demonstrate the availability of adequate methods for widespread detection of GMM phenotypic and marker stability, as this will also be required for post-implementation monitoring. Therefore, this will be an opportunity to develop high-throughput monitoring methods and procedures that will also be useful post-implementation. Plans for ongoing environmental monitoring must be feasible and case-specific, focusing on any concerns identified in science-based RA. Monitoring should be considered in a few areas outside of the release sites as well as within them. This will make it possible to detect any ecological impacts in the surrounding environment, which could be caused by the movement of the GMMs outside of the human-dominated test site(s). Researchers and regulatory authorities should agree on a feasible monitoring plan prior to executing this phase.

As indicated previously, the evaluation of health and environmental monitoring data will be aided by the availability of appropriate baseline data obtained before release (such as seasonal vector and disease patterns, use of conventional vector control methods, and local ecology), and must be considered in comparison to untreated control sites (see Section 2). Impact on transmission of the target disease(s) should be monitored by active surveillance (Section 2), but researchers should also consider using passive surveillance as a safety precaution to track the incidence of other diseases known to be transmitted by the GMM species. Measurement of disease impact will involve a component of human subjects research, which should be conducted according to the standards for clinical trials (Sections 2 and 4). At this phase, a DSMB must be in place to regularly review any adverse event reports and provide independent oversight of human safety and efficacy *(96, 97)*.

A mitigation or remediation plan may be part of RM. If so, a plan on a scale commensurate with the anticipated GMM spread and dispersal should be agreed upon with the authorities and available prior to field release. This should include agreeing on the events that would trigger implementation of the plan and ensuring that the necessary management measures, quality control and SOPs are

in place and sufficiently tested to provide confidence in their utility. The choice of mitigation or remediation method will be dependent upon the predicted harm. If the overall effect of the GMMs is beneficial, it may be possible that a particular harm can be mitigated without the need to stop or reverse the GMM intervention. If not, the minimal appropriate measure would be to stop the GMM releases. In the event that monitoring detects that an otherwise unmanageable and unacceptable harm has developed, a more extensive and intensive conventional control strategy may be required to eliminate any residual population of GMMs after release and dispersal. In the case of GDMMs, control with conventional tools will become increasingly difficult, with the potential for expanding spread and dispersal. If the RM plan involves implementation of new control measures, regulatory approval for their use should be gained before or in parallel with the investigational GDMM product. Resources to implement the mitigation or remediation plan, including staff training, should be in place at the beginning of the trial and maintained for the duration of the post-trial monitoring period.

Unintended transboundary movement (Section 5.3.6) becomes a more likely hazard with the expanding scale of field testing. This could occur through natural dispersal or through human-assisted movement, either accidentally or through deliberate unauthorized transfer. The dispersal distance and transport routes by which GMMs could reach national borders should be considered when planning the location of early trials. Geographical barriers and areas that are unsuitable for host finding or breeding often limit movement *(98)*. In early small releases, a treated barrier area downwind may reduce the chance of successful movement towards a border. Monitoring should aim to achieve an appropriate level of sampling efficiency. With GDMMs, the spread of the transgenic construct within connected populations by mating may be expected to increase the occurrence of transboundary movement. Management may become more complicated if trials of different GDMMs are being regulated by different countries within the same region.

These possibilities suggest the utility of regional authorization and oversight mechanisms for releases (Section 5), and may require provision for monitoring in countries neighbouring the country hosting the release. If desired by neighbouring countries, methods for monitoring should be put in place to track dispersal and detect transboundary movement. Agreement on appropriate mitigation or remediation methods may also need to be obtained on a regional, as well as national, basis.

Trial conduct and data analysis

Phase 3 is envisioned to involve a series of open releases of increasing size, duration and complexity. Multiple small-scale releases under various conditions will likely be required in order to collect the data necessary for planning a large-scale trial for epidemiologic impact. Table 3.3 describes the possible GMM functional and behavioural parameters of interest in this phase. The most relevant characteristics should be prioritized on a case-by-case basis, according to the type of GMM.

In addition to observing the GMMs' effects on the mosquito population structure, environmental monitoring might include ongoing observation of a manageable number of "sentinel" NTOs with a predicted high exposure to the GMMs; however, the complexities associated with interpretation of the ecological effects described for Phase 2 are likely to be even more pronounced given the broader geographical scale of Phase 3 trials. The focus should be on any specific items of concern identified by the RA, taking into account pathways to harm relevant to national or regional protection goals.

Table 3.3. Example parameters that may be relevant in open field studies as part of the RA of GMMs[a]

Parameters	Example hazards	Assessment methods	Assessment endpoints
Population size	Increased vector abundance; ecosystem disruption	Field population monitoring; population-level modelling	What is the impact of the release? Relationship between release rate, timing, method and outcome?
Density dependence	Increased vector abundance; ecosystem disruption	Comparator studies at a range of densities in laboratory; field population monitoring; population- level modelling	Does the transgenic strain differ significantly in the role of this ecological process?
Spatial distribution	Increased vector abundance; ecosystem disruption	Field population monitoring; population-level modelling; life table experiments	Limits to the spread of the transgenic organism? Rate of spread of the transgenic insect, under a range of conditions?
Vector capacity	Increased transmission per bite; increased biting rate	Comparator studies; post-release monitoring	Is the capacity to harbour and transmit pathogens increased?
Behavioural resistance	Change in behaviour that avoids, or reduces efficacy of, conventional management	Comparator studies; cohort studies on behavioural changes in different life stages; post-release surveillance; population-level modelling	Under field conditions, what limits the appearance and spread of resistance due to mosquito behaviours? Is there potential for assortative mating in the field?
Biochemical resistance	Change in physiology that avoids, or reduces efficacy of, conventional management	Comparator studies; cohort studies on physiological changes in different life stages; post-release surveillance; population-level modelling	Is the likelihood or rate of resistance development enhanced in transgenic mosquito strains?
Mass rearing quality indices	Quality of released insects is different from planned, affecting negative outcomes	Cohort experiments; comparator studies before release; operational design and audit; pre-release monitoring; post-release monitoring	Do specific aspects of released mosquito quality affect mosquito densities, pathogen transmission and transgene stability?

[a] RA should build on evidence regarding the potential hazards indicated during Phase 1 and Phase 2 trials, the methods to measure those hazards and exposure assessments. Comparator studies aim to compare the GMM with a conventional (unmodified) counterpart.

For GDMMs, a failure of self-sustaining approaches could result from the selection or evolution of mutations in the mosquitoes that reduce the efficacy of the drive or the effector mechanism (Section 2.4.4). For sterile or self-limiting approaches, incomplete penetrance of the modification may limit the potential for disease reduction. Phase 3 studies should enable observation for such effects. Phase 3 may also provide an opportunity to detect whether changes develop in the pathogen that decrease the efficacy of population replacement strategies – an effect that may be difficult to determine in short-term trials. Any such observations can feed back into models that predict the GDMMs' behaviour and functionality to inform decision-making about implementation (Section 3.6).

Phase 3 also provides a greater opportunity to evaluate the performance of the GMMs integrated with complementary conventional control actions. However, considerations for environmental variability and reduced control of experimental variables, and the impact of these on proper experimental design and statistical power become ever more influential in these progressive open releases.

3.8.4 Phase 4 – Implementation and post-implementation

At the end of Phase 3, the GMM product stands on the verge of routine use as a public health intervention. Sufficient data should have been collected to understand the effects of the GMMs on disease transmission, ecological interactions, and the spatial characteristics of dispersal and transgene persistence. Monitoring mechanisms will have been developed. Experience with quality control and assurance requirements will also have been accumulated in Phase 3 to further inform the planning for scale-up production. Assessment of the performance of the RA and RM strategies in Phase 3 will play an important part of any decision to move forward with wider implementation – a decision that will necessarily also take into account broader cost–benefit, acceptance and national public health goals (Section 1).

National regulatory authorities will take the results up to this stage into account when making decisions about whether to recommend large-scale deployment of GMMs in their countries. National public health agencies should also consider the results of risk analysis in deciding whether to adopt GMMs as a component of their national disease control programmes. Countries may consult the WHO evaluation process *(99)* for guidance on the use of GMMs as a public health tool. The African Vaccines Regulatory Forum *(100)* provides a potentially relevant model for enabling timely regulatory evaluation and decision-making among national authorities. Efforts within the African Union to establish an African integrated vector management (IVM) platform will also be relevant *(101)*.

At this point, RA and RM should be incorporated into broader risk–benefit and cost–benefit analyses to provide the framework for quantifying the appropriate (health, economic) returns of a GMM release programme. Such analyses could be done during or after Phase 3, at a point when sufficiently reliable information about the utility of the GMM enables projections of cost and benefit. It should be noted, however, that increased experience with wide-scale implementation in Phase 4 may result in delivery improvements with associated cost reductions.

RA for implementation and post-implementation

As in earlier phases, RA must be case-specific and science-based. During the RA for implementation, it will be important to review the cumulative risk analysis experience from prior testing. Considerations will include whether hazards were fully identified, risks were accurately characterized, and relevant management measures were effective. By the time a GMM approach is contemplated for implementation, substantial efficacy and biosafety performance data will be available. Computational modelling will take advantage of these data for predicting optimal delivery regimens and wide-scale effects. However, a remaining uncertainty may be related to long-term performance and the associated risk of failing to meet the product's claim of disease control.

The GMMs' phenotypic, behavioural and population-level effects on the target mosquito population should be re-assessed within the scope of risks associated with full public health implementation scenarios. The RA for Phase 4 should identify GMM characteristics that might change as a result of

mass production in a way that impairs the intended effect of the GMMs, including selection for altered development rates and marker expression. Consideration should be given to the quality control standards for maintaining GMM characteristics and procedures (for example, in rearing mosquitoes for release programmes, determining sex ratios for release, etc.) in order to ensure that processes remain relevant to the RA assumptions throughout the release programme.

Failure to maintain the intended effects on the target vector population has been raised as a long-term concern, albeit one shared with other common control methods. Mutations that confer resistance to insecticides are well-known. It has been demonstrated that mutations favouring resistance can be present in populations before the start of a control intervention programme *(102)*. Widespread deployment of GMMs will increase the possibility that pre-existing genetic variants conferring functional resistance will be encountered within the target population, and these may proliferate due to competitive advantage. Moreover, the potential for evolution and adaptive processes could include the evolution of resistance to the transgene function within the target mosquito population, the evolution of the disease pathogen to resist transgene function, or changes in the behaviour or host range of the target mosquito species. RA should predict the likely manifestation of any potential resistance *(41, 103)*, which will be highly dependent upon the particular GMM technology. Modelling will be useful in this regard (Section 3.6). RA for Phase 4 must take into account any specific plans for ongoing monitoring of the GMMs' functionality (Section 2).

Additional hazards to human health should be considered in the risk analysis for Phase 4. The release of transgenic mosquitoes may raise the concern that existing control measures could be reduced, either as people become lax about personal and household mosquito control efforts or as governments look for cost savings. The implications of a potential reduction in conventional vector control for mosquito population dynamics, human health and the wider receiving environment require appropriate RA and RM. The possibility of a resurgence of disease when immunologically naïve human populations are exposed to disease after a prolonged period of low incidence is a concern that should be assessed in post-implementation monitoring. Again, this risk is not unique to GMMs. For example, concerns were initially raised over the possibility that ITNs might increase mortality in older children through delayed acquisition of immunity to malaria. Empirical evidence from a community-randomized controlled ITN trial in malaria holoendemic western Kenya found no evidence that human immunity to blood-stage antigens was compromised in young children after two years of ITN use *(104)* and no evidence of increased all-cause mortality in older children six years after ITNs were provided to children *(105)*. However, observations of increased susceptibility in older children and adults following long-term ITN use have been reported *(106)*.

RA in this phase must consider the likelihood and consequences of mosquitoes spreading across international borders, especially in the case of GDMMs. It would be appropriate to seek the views of authorities in neighbouring countries on hazards to include in the RA. At this point, the possibility of unauthorized human-assisted introductions into new territories in order to gain benefit from the GMMs should also be kept in mind as a possibility, since the presence of the GMMs will be unrestricted. RA should consider whether there are any remaining science-based reasons to continue environmental monitoring.

Risk management

At the implementation stage, most management activities are expected be national responsibilities, according to the pattern of other public health interventions. The decision on responsibilities

for RM will be made by the relevant regulatory authorities. RA will determine the need for RM, which should be proportionate and directed at specific hazards. RM will largely consist of post-implementation monitoring and surveillance to address any remaining uncertainties identified in the RA and/or to confirm at the operational level that the conclusions of the earlier RAs were accurate. It should also ensure that operational scenarios are proceeding as expected and identify areas where poor efficacy is observed related to heterogeneous conditions or appearance of resistance. RM planning for post-implementation monitoring should focus on appropriate effects and variables based on the previous RAs and trial data, duration of the surveillance, geographical limits to surveillance, and methods by which to measure the effects. By this phase, the necessary monitoring methods must be easily scaled up and applicable in the field. Monitoring of GMMs' effect on health should be integrated into national disease control programmes in the implementing countries or regional control programmes.

RM will also involve plans for quality control in rearing facilities to monitor for any signs of failure of the mechanisms integral to the efficacy of the GMMs or factors that could make control more difficult. In this event, RM might include breeding schemes to refresh background genetics.

A potential subject of ongoing monitoring could be the effect on the local mosquito community structure, including the presence of the transgenic construct in other mosquito species. If part of the intended effect is the crossing of the gene drive product into related vectors within the species complex, the ability of the gene drive to effect population suppression or replacement should also be monitored in those other species.

A need is anticipated for ongoing monitoring to determine whether the GMMs' effectiveness has diminished with time or unexpected effects have become evident upon widespread use or use in new areas (Section 2.6.4). Post-implementation monitoring for GMMs should be done in the context of experience with other vector control tools. For example, the loss of efficacy due to selection for resistance is a general challenge for insecticides and drugs *(107, 108)*. A loss of efficacy for GMM tools, while an undesirable outcome, should be viewed with that previous experience in mind. RM in this regard involves the use of GMMs in conjunction with multiple mosquito and disease control methods, which is expected to mitigate the risk of disease resurgence should GMMs or other tools lose efficacy.

If continued ecosystem monitoring is required by regulators, it will be important for parties to agree beforehand on what is to be monitored, to what extent and by whom; how the data will be collected and analysed; and what circumstances would trigger responsive action. There should be a rationale in each of these cases whereby monitoring focuses on valid harms to the ecosystem identified in the RA. Relevant parties must agree on biological endpoints of concern, which should be chosen based on their potential for harm and not simply as indicators of ecosystem change. When GMMs are deployed in conjunction with other tools for vector control, such as insecticide applications, it must be remembered that these tools themselves could also have an effect on the ecosystem, making it difficult to attribute any observed changes to the GMM product.

General surveillance approaches are unlikely to be effective or informative in determining the need for risk mitigation. Decisions on longer term environmental monitoring should keep plausibility, feasibility and interpretability well in mind in considering how results will inform response decisions. If required, such monitoring should focus on a few selected organisms identified as the most likely to interact with the target mosquito species. The RM plan must

establish and delimit appropriate time intervals for reviewing the impact and continued safety of the GMM technologies. The plan might also include agreement on conditions under which monitoring could be stopped if no adverse effects are observed.

Monitoring will trigger responsive action if the measured parameters are outside the accepted range. The RM plan should include tracking of metrics that would trigger a mitigation or remediation plan. The determining factors for instituting such a plan should be agreed upon in advance of implementation. RM planning should be done in consultation with regulatory authorities and be clear on where responsibility for surveillance and response would lie should an adverse effect be detected. The appropriate regulatory structures, mechanisms and methods need to be in place as an integral part of the RM. The post-implementation surveillance method and risk mitigation measures should also be reviewed at appropriate intervals as GMM population levels change.

Since RM activities at this phase are likely to require transboundary cooperation, it will be important to consider how neighbouring national authorities will plan and carry out RM actions, including the appropriate surveillance that might be needed. The intentional movement of transgenic material across national/international borders is governed by established administrative procedures under the Cartagena Protocol on Biosafety (CPB) *(4)* (Section 5), supported by RA and RM measures. Parties bound by the CPB (and its instruments) are expected to carry out the movement of transgenic material (to both Parties and Non-Parties to the Protocol) in accordance with the objectives of the Protocol (Section 5) and other regional agreements. There are also provisions in the CPB dealing with unintentional transboundary movement. These provisions should be considered governments' minimal level of obligation to their neighbours. Regional coordination of RM activities would be desirable.

3.9 Safety review

Safety review will be conducted at many levels, including by institutional biosafety committees (IBCs) *(109)*, institutional ethics committees (IECs), DSMBs, national competent authorities, and/or regional or supranational agencies (Section 5). Countries that are signatories to the CPB are expected to establish national legislation and national biosafety authorities for the oversight of GMOs. WHO has mechanisms for the review and prequalification of new vector control products (e.g., WHO Vector Control Advisory Group https://www.who.int/groups/vector-control-advisory-group and WHO Prequalification Team: Vector Control Products https://extranet.who.int/pqweb/vector-control-products) *(99)*. Especially in the case of self-sustaining, non-localizing GDMMs, conduct of an external all-hazards RA by qualified individuals with no vested interest in development of the product, which is made publicly available, has been recommended *(40)*.

3.10 Impact assessment

In addition to the project-specific technical RA described above, the regulatory authority may also require an impact assessment (IA). The need for and extent of this requirement may be legally defined and influenced by the perceived potential for adverse effects. Some jurisdictions limit IA to the analysis of impacts on the biophysical environment, while others include the social and

economic impacts of the project. This impact-based assessment will focus on potential adverse, neutral or beneficial changes that could result from the project *(110)*. It may include consideration of reasonable alternatives to meet the stated need. Components might include: ecological IA to examine potential effects on habitats, species and ecosystems; health IA to examine potential effects on the health of the population and distribution of those effects within the population; and socioeconomic IA to examine potential social, economic and cultural effects on the lives and circumstances of potentially affected people and communities *(111–113)*. Ecological and health IA should be informed by the RA. However, health considerations might extend beyond the impact on vector-borne diseases to include, for example, potential psychosocial and mental health effects of the project on the community. Socioeconomic IA might consider issues such as the potential for disruption of livelihoods or social cohesion, equality of benefits, and effects on cultural heritage. Concerns and perceptions of affected stakeholders should be considered, even when not supported by technical RA.

IA is intended to provide a mechanism for arriving at an optimal decision regarding the implementation of a technology. Common steps in an IA include: 1) defining the scope of the assessment; 2) determining baseline conditions and identifying important potential adverse, neutral or beneficial changes that could arise; 3) developing management plans to avoid or reduce any predicted adverse impacts; and, if the project is approved to proceed, 4) monitoring its impacts. An important objective of IA is to integrate the input of stakeholders in the area of interest into project design and decision-making. Thus, public involvement is a prerequisite for effective IA.

3.11 Co-development and capacity strengthening

The successful implementation of GMM interventions requires transparent, focused, proportionate and credible biosafety assessments. National biosafety authorities or committees, capable of providing appropriate independent guidance and overseeing all facets of testing and implementation, will be important for biosafety assessments of GMMs and for decisions on appropriate levels of RM. National biosafety authorities or committees should draw on the available expertise across a wide range of scientific, health, environmental and economic disciplines to assess the risks of GMM technologies, as, for example, in the CTNBio in Brazil (http://ctnbio.mctic.gov.br/en/inicio), CIBIOGEM in Mexico (http://www.conacyt.gob.mx/cibiogem/index.php/cibiogem) *(114)*, or the Burkina Faso Agence Nationale de Biosécurité. The intended public health applications of GMMs make it critical to involve institutional or national ethics committees and health regulators in decision-making for field testing. Stakeholder groups potentially affected by GMM releases provide insights into community values and concerns relevant to potential releases, and they should have a consistent and strong voice in both biosafety and benefit analyses associated with the testing and implementation of GMMs (Section 4).

The regulatory and decision-making bodies responsible for biosafety should have the capacity to formulate the risk problem, define appropriate endpoints for risk, interpret the character of the component sources of risks, interpret the quantification of risk components, and understand the efficacy and uncertainty related to proposed RM measures. This capacity will build upon experience with other types of products, especially GMOs, e.g., *(115)*, and public health tools.

However, in many cases, there will be a need to provide additional information and/or training on issues particular to the evaluation of insect products. Where this capacity is not available at the national level, efforts should be made to strengthen the necessary national expertise and to obtain independent international expertise where necessary.

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4. Ethical considerations

SUMMARY

The development, testing and introduction of GMMs for the control of vector-borne diseases raises ethical and governance issues that warrant careful deliberation, particularly for GMMs with gene drives designed to spread and persist in the environment. Researchers will need to consider the motivation for conducting the research and its purported social value; the relationship between humans and the environment and how the research figures into that relationship; and how the risks and benefits of GMM research will be assessed, managed and discussed with communities, stakeholders and publics. Researchers should ensure that coordination and communication with communities is fair and culturally appropriate, and that community values and concerns are taken into account in research plans at all stages. Ethical GMM research will attend to considerations of justice and equity, and fulfil obligations of transparency, capacity strengthening, benefit sharing and ongoing stewardship.

Respect for communities should be an overarching ethical goal in GMM trials. Community engagement will play a central role in demonstrating respect for affected communities and fulfilling ethical responsibilities to them. Individuals whose role falls within internationally recognized standards for human subjects research must be protected accordingly and, as appropriate, individual or household-level informed consent must be sought. GMM research should also recognize ethical responsibilities that extend beyond standard compliance criteria. Engagement with a broader set of stakeholders and publics is important for realizing research goals, especially in the development of new technologies. Sincere and well-developed engagement can help to direct technical and public health goals, reduce the chance of misunderstanding of the science needed to meet the goals, and improve the performance of the research project in both technical and social respects. Community and stakeholder engagement should be undertaken early, at the start of the phased testing pathway for GMMs, and be tailored, iterative and sustained.

Scientists from countries where GMMs are intended to be used must be involved in all facets of the research in ways that promote leadership and co-ownership of the technology.

The development, testing and introduction of GMMs for the control of vector-borne diseases raises ethical issues that warrant careful consideration. There is a perception that the issues are novel, likely owing to the novelty of the technology *(1)*. New technologies can induce fear and distrust because of the uncertainty around their purported risks and benefits. Innovations that have the potential to impact cultural identities tend to generate intense social concern *(2)*. However, the ethical issues around GMMs are not new, in that, the concern for the respect and welfare of humans and the environment that evokes considerations of justice, transparency, risk and benefit is also salient in other research contexts involving other technologies. Rather than novel, these ethical issues may be more aptly characterized as being highly contextual, requiring consideration through an applicable socio-cultural lens.

GDMMs raise governance issues that are new, given the practical and procedural challenges posed by their potential to spread and persist in the environment *(3, 4)*. Governance frameworks, through which elements of society are able to exercise authority in decision-making on issues affecting public life, may need to be adapted or modified to be more responsive to the issues raised by GDMMs. The development and introduction of GDMMs for control of vector-borne diseases will involve interaction with a diverse spectrum of groups, including communities, researchers, funders, national and international authorities at multiple levels, and broad alignment of public engagement efforts, biosafety, and regulatory and ethical standards *(3, 5)*.

Compliance with regulatory requirements that govern the conduct of research is mandatory (Section 5). It is a standard requirement to obtain ethical clearance for any research involving

Key points

- **GMM research involves ethical responsibilities that extend beyond standard regulatory compliance.**
- **The ethical justification for GMM research must be its scientific and social value; in making risk vs. benefit decisions, the opinions of those who will be most impacted should be prioritized.**
- **Uncertainty around the potential risks or benefits of new GMM technologies does not mean that they should be avoided; there is no reason to assume that current or familiar interventions are safer or less risky than new ones.**
- **Ethical obligations to those living at or near the trial site may be met by informed consent or community authorization mechanisms depending on their level of involvement.**
- **Community engagement should begin in Phase 1, with those living at sites where the GMMs will be developed and tested; a co-development approach that emphasizes authentic partnership and knowledge engagement is recommended.**
- **Both ethical clearance and government permission will be required for testing to proceed.**

human participation. The process for doing so may differ among countries; in some, this process may require considerable lead time that must be factored into planning. International standards for research conduct include submission of protocols for the involvement of human subjects, as well as biosafety and the use of animals, to appropriate oversight committees that are formed according to national policies and regulations (Section 5). However, researchers should not assume that regulatory compliance implies that ethical responsibilities have also been adequately addressed. Broader ethical issues and responsibilities are expected to arise in the context of GMM trials that are not specifically mandated by administrative law or organizational policies. There is ample evidence that simply conforming to regulations and institutional policies does not always satisfy public expectations and researchers' obligations.

To address both science-based and values-based concerns, appropriate governance may need to draw on mechanisms that go beyond those prescribed in currently applicable regulatory and policy frameworks *(5, 6)* (Section 5), such as commitment to best practices and community standards *(7–10)*. Importantly, efforts and resources need to be mobilized to support low- and middle-income countries in strengthening their capacity in research governance *(11, 12)*.

4.1 Role of ethics and engagement in science and technology

Ethics calls attention to the concepts of right and wrong, and can imply a higher and more rigorous standard than that of civil authority. Regulations, laws and organizational policies dictate standards and procedures with which individuals and organizations must comply. By contrast, ethics can be understood as activity or inquiry that aims to shed light on the correctness or justifiability of some conduct. In the context of GMM trials, ethics aims to establish the correctness of certain procedures (e.g., engagement, consent, evaluation of risks, benefits, safety, etc.) and to understand the interests of stakeholders and their various entitlements, rights, or other types of claims and obligations, and how these relate to the overall mission of public health – which is to protect and improve the health of people and their communities *(12)*.

Scientists have long appreciated the importance of public dialogue and outreach to realize the envisioned results of their research. For those undertaking work on the cutting edge of discovery or technological capability, there can be both positive and negative implications for paying attention to the reaction and receptiveness of the broader public. On the positive side, engagement with people not generally considered to be part of the research community can both enrich the research process and provide access to information and perspectives that would have otherwise been unavailable to the researchers. This engagement is, for example, integral to risk analysis and IA (Section 3). It can also inform goals within the target product profile and thus help in achieving the broader impacts researchers seek. Moreover, scientists have become cognizant of new ways that involving non-scientists can be beneficial. Engaging non-scientists in collaborative or problem-solving roles has led many to envision a new era of science in which many people can be enrolled in cooperative projects as "co-producers" of new knowledge *(13–15)*. On the negative side, research that comes under public scrutiny can become the target of organized opposition that has the potential to frustrate not only the application of science, but even the research process itself. Sometimes, opponents of science and technology are simply pursuing interests that are genuinely contrary to the advancement of a given technical project. However, sincere and

well-developed engagement that acknowledges and demonstrates respect for these perspectives may reduce the chance that opposition is based on a misunderstanding of the science or its goals.

Many scientists view the public communication of science and technology as a key responsibility, in accordance with the central tenets of responsible research and innovation *(16)*. In this vein, scientists have obligations to reflect on the implications of their work and possible alternatives; satisfy elements of transparency and responsiveness; and promote a positive and reciprocal relationship between science and society *(16)*.

4.2 Ethics issues

4.2.1 Motivation and social value

It is important to consider the ethics issues that will inevitably arise at each phase of the development and testing pathway (Section 1) for the successful implementation of GMMs. Many of the issues will be pertinent at every phase as the research progresses, as components of RM and risk communication, and will need sustained efforts to ensure that ethical responsibilities are met. However, one important issue that requires reflection at the start, or even prior to initiating laboratory studies, is the motivation for the research and the social value it purports to attain.

Scientists have a moral responsibility to consider the implications of their research, including the design choices they make and, more broadly, its impact on society. This is especially salient for GDMMs that could have far-reaching and widespread consequences, some of which might be irreversible and negative. Research involving GMMs for the control of vector-borne diseases should be motivated by, and aim to promote, social value *(7, 17)*.

Making explicit the social value and purpose of a scientific research project initiates broader reflection that serves several key functions. First, an explicit discussion from the outset of how research will produce beneficial outcomes can yield unexpected improvements in project design. Conducting such discussions with project team members, advisors and consultants increases the range of knowledge and interests that can be incorporated into the research design, helping to ensure that important strategies or alternatives are not overlooked. This helps researchers to avoid losing time by pursuing strategies that may be technically feasible, but that cannot be implemented due to their incompatibility with social mores, legal mandates or other elements in the practical infrastructure. Second, public presentations of a project's motivation, goals and ethical vision, and explicit articulation of the ethical considerations guiding the scientific work and its relationship to various social goals disseminate this thinking to a broader audience and may prove important in building trust and cooperation with host communities. Finally, the public record that is created by documenting how and why the science was done creates an opportunity for others to learn. Canada has pioneered approaches to embed such activities within large-scale research projects dedicated to biological research *(18, 19)*, and some of these may serve as useful templates for GMM trials.

Most scientists view their work as having value and a social purpose, and this may be especially so for those conducting research on public health and disease control. In contemplating the potential social value of GMM research for vector-borne diseases, it is useful to think beyond immediate impact and articulate how the potential beneficial outcomes of the project contribute to the broader aims of the global public health agenda, such as disease

elimination *(20)* and sustainable development *(21)*. Vector-borne diseases disproportionately affect the poor and those facing conditions of social injustice, e.g., gender inequality, limited access to health care and education, and the absence of other opportunities that support human flourishing. In addressing these diseases, the potential social value of a GMM vector control strategy is amplified by its contribution to the Sustainable Development Goals (SDGs) of elimination of poverty (SDG1), promotion of health and well-being (SDG3), access to education (SDG4), gender equality (SDG5), and reduced inequities (SDG10).

4.2.2 The human–environment relationship

Humans have a complex relationship with the environment, variably acting in ways that either instrumentalize nature or protect it. Genetic engineering complicates this relationship by introducing the ability to do both things at once. Both GMM strategies (population suppression and population replacement) test the relationship between humans and the environment. Population suppression theoretically permits the elimination of vector species, an outcome many find objectionable owing to the belief that all species have intrinsic value *(22)*. Population replacement may permanently alter the genome of the vector species, inducing the kind of evolutionary change some find unnatural *(23)*. It is the self-sustaining, non-localizing (low-threshold) gene drive that could have the most profound impact on the environment and gives us most pause to examine this relationship *(3)*.

Ecocentric views of the natural world are likely to clash with worldviews that are more anthropocentric *(6)*. There is no way to resolve conflicts about deeply held philosophical and cultural beliefs regarding the moral status of species *(23)*, or their rightful place and that of humans in a shared, complex and interconnected environment. There are, however, two ethically significant points to consider in the context of GMM research. First, judgements about interventions based on characterizations of what is natural or non-natural should be avoided *(12)*, since provenance has no bearing on an intervention's potential for harm or benefit; for example, vaccines are not natural, but pathogens are. Second, in accordance with the principle of justice, the opinions of those most impacted by a GMM release should hold the most weight, since they bear the bulk of the associated risks and burdens.

In the case of the proposed use of GDMMs to combat malaria in Africa, problem formulation workshops held by the African Union Development Agency – New Partnership for Africa's Development (AUDA-NEPAD) found that "there was a general consensus among participants that reducing or eliminating mosquitoes for the benefit of human health was acceptable and consistent with historical practices to control malaria" *(24)*. While this expressed worldview may clash with sentiments found elsewhere in the world, it would be ethically inappropriate to not prioritize African views over those of others in this case; it would also be inconsistent with the goals of authentic community engagement (Section 4.3). While it is important to acknowledge and respect the multiplicity of views on the delicate relationship between humans and the environment in relation to GMM release, priority must be granted to the views of host communities as a matter of respect and justice *(6, 25)*.

4.2.3 Risks and benefits

GMMs are population-level interventions. In GDMM trials, the product is expected to spread to some degree (Section 1). This feature of GMMs may yield both positive and negative aggregate

effects. Risks and benefits have impact at a collective level, and the impact on communities can persist and increase over time *(9)*.

The scientific and social value of the research provides the ethical justification for proceeding with research when individuals and communities are exposed to potential risk *(12)*. However, potential benefits should outweigh potential risks. RA (Section 3) emphasizes the importance of the phased and incremental roll-out of GMM products along the development pathway in order to carefully mitigate risks. Conducting testing incrementally (i.e., proceeding to increased levels of human and environmental exposure only after fulfilling agreed upon safety, efficacy and acceptability criteria in the previous phase) should include an independent and thorough all-hazards RA. The importance of RA at the end of Phase 1, prior to moving to field testing, is emphasized particularly for self-limiting, non-localizing GDMMs. Furthermore, risks should be evaluated on a case-by-case basis, accounting for health, environmental and socioeconomic risks, and grounded in the protection goals established by host countries (Section 3). This approach is also consistent with applying an ethical lens that is sensitive to context.

Since mosquitoes are capable of unpredictable movement among locations, it will be impossible to identify in advance all persons with whom they might come into contact. In the general case of vector biology research, it has been proposed that biosafety oversight may be a more appropriate model than individual human subject protection because risks and benefits are likely to be assumed by whole groups or populations *(26)*. Lessons may be drawn from environmental health programmes, which usually characterize risk in epidemiological terms that make it difficult to describe the exact causal mechanisms of exposure or to translate population-based exposure calculations to the individual level. Additionally, these programmes consider how risks may be distributed across economically, politically or ethnically vulnerable populations as an issue of environmental justice. There are no analogues to environmental justice in standard human subjects research ethics *(27)*, but appealing to concepts of justice more broadly, particularly in a public health context, is appropriate (Section 4.2.7). The similarities with environmental health programmes suggest that GMM trials, which involve exposure to potential environmental hazards, should incorporate ethical perspectives beyond those considered in human subjects research.

A balanced ethical evaluation will need to carefully consider the benefits of GMM release. There is increasingly greater emphasis placed on how a research activity is intended to benefit parties that will be exposed to the risks *(28)*. Assessment of health, environmental and socioeconomic benefits should be undertaken and considered alongside the risks.

Socioeconomic IAs (Section 3) follow a prescribed methodology that seeks to identify and evaluate the impact of a proposed intervention on the social and economic aspects of people's lives and circumstances *(29)*. Risks to social cohesion or employment opportunities, for example, might be evaluated. In a similar vein, the socioeconomic benefits of a successful GMM release, i.e., a safe and effective vector control strategy, can also be assessed. For example, IA could evaluate the potential for improved economic prospects for women if malaria elimination is achieved. Vector-borne diseases disproportionately affect the poor, and women and young children are more vulnerable to diseases such as malaria and Zika. Pregnant women infected with malaria are at higher risk for severe anaemia and maternal death, as well as miscarriage and neonatal death *(30)*. Children are the primary victims of malaria. Mothers who are the usual caregivers are unable to pursue education and gainful employment opportunities outside of the home if they must remain inside to care for sick children. Eliminating malaria would yield health benefits for children, but also extended socioeconomic benefits for their families.

Determining how benefits and risks will be distributed and how they will impact different stakeholders and members of the population is essential at each phase of the development pathway, from end to end. At the start, during laboratory studies, consideration should be given to how co-development of the technology will occur and what opportunities might be available to research partners and early career scientists for strengthening capabilities. At the end, during post-implementation, consideration should be given to how surveillance activities will affect communities. Making these determinations requires transparency in planning (Section 4.2.5) and engagement with stakeholders (Section 4.3). Throughout the testing pathway, RM will be key, as will the sharing of any interim benefits, e.g., sharing of outputs and credit for knowledge generation.

The prospective assessment of the risks and benefits of unpredictable and uncertain occurrences along the development pathway emphasizes the importance of data sharing and modelling in order to provide the data inputs needed to support such assessments *(8)*. Uncertainty around the potential risks or benefits of a novel technology does not mean it should be avoided *(31)*; every technology has unpredictable risks and benefits when it is new *(23)*. Decision-makers should guard against the common assumption that current or familiar interventions are safer or less risky than new ones (*12)*. Choices about risk tolerance have ethical importance, as both action and inaction can have dramatic impacts on the lives of people *(32)*. It is, therefore, important to weigh the harms avoided by foregoing the use of new, seemingly risky technology against the harms incurred by failing to use it *(12)*.

4.2.4 Consent

In GMM trials, there is a wide range of interactions with the host community. Simply living in the vicinity of a GMM release is insufficient grounds to require informed consent from any individual for an open release of mosquitoes. Community engagement provides a mechanism for addressing obligations to respect the interests of those within communities that may be associated with or affected by the research. For GDMMs intended to spread and disperse, predictions from computer simulation modelling of the release can help to identify communities with which to engage. However, interactions with individuals and households for the purposes of data collection in trials with both entomological and epidemiological endpoints are likely to give rise to individual or household-level identifiable data; in the absence of specific exceptions or waivers, such interactions will require informed consent *(33)*.

Informed consent

Informed consent is universally recognized in research ethics regulations as a necessary protection for human research participants (see below and Section 5). Informed consent is a process intended to ensure that those who will be observed or involved in a research activity are fully and explicitly advised of all risks, costs or inconveniences they may bear as a result of participating in the research, and voluntarily agree to accept or bear those risks and costs, in addition to any potential benefits they might obtain. Some commentators have argued that informed consent will be necessary to ensure that GMM trials are conducted ethically, and that it is an important mechanism for demonstrating respect for the autonomy of persons. However, the precise circumstances under which informed consent must be obtained in GMM trials, and from whom, require careful consideration.

In some cases, it can be ethically acceptable to conduct research without obtaining individual informed consent, such as when the nature of the research makes it impracticable to seek consent (e.g., a study that involves secondary data analysis of a large cohort where it is no longer possible to locate the participants); when consent is not required; and when there are other processes in place that can serve the same function (e.g., notification and implied consent with ethics committee approval), so long as protections for human subjects are in place *(12, 34)*. Competent adults may be exposed to experimental public health interventions without their consent in population-based research *(34)*. GMM field trials are an example of the first case, where obtaining individual informed consent is impracticable, and absent data collection activities are also an example of the second case, where individual consent is not required.

Research ethics guidelines and regulations generally rely on four criteria to determine whether an individual is a research participant and, therefore, should normally give informed consent as a condition of their participation: 1) if an individual is directly intervened upon by an investigator; 2) if an individual is deliberately intervened upon via manipulation of the individual's environment by an investigator; 3) if an individual interacts with an investigator for the purpose of collecting data; or 4) if an investigator obtains identifiable private information about the individual for the purpose of collecting data *(35)*. At any point along the testing pathway for an investigational product, individual informed consent is required from those who meet the internationally accepted criteria of human research subject. Caged field trials or small-scale and large-scale open releases of GMMs in the context of a research trial do not satisfy the requirements of the first two criteria, since no individual is intervened upon directly or deliberately, even if they live in close proximity to the cages or release sites *(33)*. The third and fourth criteria focus on the interactions between investigators and individuals who play some special role in generating or facilitating the collection of study data.

In GMM trials, only a select few interactions are associated with data collection. In early phase trials, this would pertain to individuals who agree to complete surveys or participate in interviews for purposes associated with the research. It would also pertain to those homeowners who agree to the placement of mosquito traps for monitoring purposes, or who permit researchers access to their homes for the purpose of collecting mosquitoes. In particular, mosquito collection in homes for research purposes is likely to be linked to Global Positioning System (GPS) data, which would be required for spatial analyses of species composition and the spread of mosquitoes after releases. When these GPS data are highly precise, they will effectively tie the associated mosquito data to specific households, thus rendering the data identifiable at this level, even if they are not personal in nature. Informed consent does not necessarily imply individual informed consent. In this case, since it is the household that is identified and not an individual, the consent of the head of the household or her/his designate is more appropriate than requiring all members of the household to provide informed consent. Given the extremely low levels of risk associated with these types of data collection activities, ethics review committees, which are tasked with ensuring that proposed studies conform to internationally and locally accepted ethical standards (Section 5), might further consider modifications to normal consent procedures, such as verbal consent or full waivers of informed consent, as long as all other necessary permissions and protections are ensured.

As the research progresses along the testing pathway for GMMs and trials with primarily entomological endpoint designs begin to incorporate epidemiological endpoints, such as incidence of new infections with malaria or dengue, they are expected to require the collection of blood specimens or other forms of clinical data. In these cases, the data collected will constitute identifiable personal information and individual informed consent will be required.

Community authorization

It is important to note that researchers also have obligations to respect the interests of those within communities hosting GMM trials who, although not research subjects, may be associated with and/or affected by the research in a meaningful way. The valuable role of community engagement (Section 4.3) is emphasized here, where practices are undertaken to inform such persons about the project, and efforts are made to understand, respond to, and learn from their perceptions and reactions in a way that makes clear that their opinions have influence *(8)*. Informed consent is only one among myriad ways in which to demonstrate respect for persons and their autonomy *(36)*, and a well-designed, culturally appropriate community engagement process can help to discover people's preferences for how best to preserve and protect their autonomy in the absence of individual consent.

A GMM release is an area-wide intervention entailing risks and benefits that have impact at a collective level. However, it is prudent to exercise caution in thinking that the interests of the community are simply the aggregate of individual interests *(37)*. A process of engagement that can reflect the collective interests of the community is desirable. Researchers have a responsibility to obtain fair and legitimate authorization (variably referred to as consent/agreement/endorsement/acceptance – communities will ultimately define the appropriate term to describe their collective permission) for field testing of GMMs. How that process unfolds will depend on the values, goals and preferences of the community. Indigenous communities may look towards established processes, such as Free, Prior and Informed Consent (FPIC), for guidance on exercising their decision rights in relation to GMM release. FPIC is a mechanism for withholding or giving consent to a project that may affect ancestral lands and territories. It remains unclear, however, whether FPIC – a legal entitlement meant to ensure decision-making rights over lands and natural resources *(38)* – is an appropriate framework for GMM release. Communities may want to shape their own process to reflect more inclusive participation and co-development – two important ethical principles that underpin community-wide public health interventions, but that are not robustly characteristic of FPIC *(39, 40)*. Moreover, a community-wide public health intervention is a global public good, unlike land and natural resources. It is important to avoid processes that privilege some communities over others, leading to procedural injustice and inequity. The key message for researchers is that efforts should be made to ensure that communities, stakeholders and publics are appropriately engaged (Section 4.3), and that host communities for GMM release are given the opportunity to provide legitimate authorization for the release.

Community authorization can be thought of as representative of the informed consent goal of protecting the interests of those who will be affected by the research. The process should include communicating the aims and methods of the science and the potential risks and benefits of the project; it should also strive to achieve sufficient assurance that the community understands and has agreed that the research and public health interventions should take place.

Community authorization and informed consent share several key elements. Both promote a deliberative model for addressing ethical issues that arise in connection with research. Rather than relying on strict rules or criteria that must be followed, the deliberative approach mandates that ethical issues be considered before the research is undertaken, and periodically reviewed. Both are intended as a mechanism for demonstrating respect for persons who will be affected by a research project or a public health intervention. Both imply "voice" – an opportunity to express concerns and to receive replies that are addressed specifically to those concerns. A reply might

take the form of assurance or clarification of activities and/or risks, or a modification to the research plan that alleviates concerns. For the conditions of voice to be fully met, affected parties must accept the reply offered as a satisfactory response to concerns. The research should not continue unless or until such authorization has been obtained.

Community authorization differs from informed consent in several respects. First, the methods of informed consent that have dominated discussion of research ethics in the industrialized world assume that consent is given or withheld by individuals. When possible, the individual in question is the person who bears the risks, but, in cases of children or people who are incapacitated, a third party is authorized to give or withhold consent on their behalf. Community authorization is a procedure intended to elicit agreement on behalf of a group, often a political community, such as a neighbourhood or township, or social group in a specific locale that shares government *(41)*. Thus, procedures for community authorization more typically rely on norms for group decision-making, such as voting, consensus or negotiations with leaders and representatives who are recognized as having the authority to speak on behalf of the community as a whole. Since norms for group decision-making vary widely, it is especially critical that procedures for identifying leaders and representatives, or for interacting with community groups, are based on detailed knowledge of the locale, its traditions, and its history of cooperation, exploitation and conflict resolution *(42)*.

Second, where there are established leaders and decision-makers in the host communities, GMM trials are likely to involve a wide range of interests spread across a number of different groups, not all of which will be governed by the same leaders. Host communities for GMM trials will most likely have multiple "layers" of authority, such as a municipal council, Chief, village elders, chamber of commerce, farmer's association, or household. As a result, researchers should be wary of uncritically assuming that any one decision-maker can provide definitive representation of a host community. One key implication for authorization is that, unlike individual informed consent, there may not be one specific mechanism or point in time at which it is granted. Instead, it is likely to be more of a judgement on the part of researchers that they have exercised the appropriate level of diligence in eliciting and responding to the concerns of the interested parties and groups, and vigilance in maintaining the necessary commitments and relationships once it has been determined that there is a general collective will to proceed. In the absence of a specific mechanism, authorization may represent an accumulation of endorsements, or willingness to cooperate with and participate in the trial in various ways, or to not actively oppose it (assent). Collectively, these activities, which are sustained over the full duration of the GMM trial from planning to post-trial negotiations, constitute community engagement (Section 4.3).

Finally, it is important to note that community engagement and community authorization for GMM trials alone will not be sufficient to allow trials to proceed; it is expected that there will be a need to secure formal government permission to work with and release the GMMs (Section 5).

4.2.5 Transparency, data sharing and coordination

The development of gene drive technology carries an obligation for transparency and accountability *(7, 8, 43, 44)*. GMM researchers should commit to being appropriately transparent about their work. This is important for earning public confidence, ensuring that the product meets stakeholders' needs, encouraging the inter-project coordination necessary for responsible field testing, and minimizing any risks to health or the environment. In interactions with the public, failure to be transparent about data can heighten anxiety by creating the impression that scientists

know things they are not willing to reveal, and this may fuel mistrust. From the perspective of product development, inappropriately conducted field trials have the potential to negatively impact the future success of other GMM products, undermine community, stakeholder and/or public confidence in the technology, and jeopardize the regulatory and funding environment. Transparency should include, but is not limited to, keeping open and accessible records of any (accidental or intended) releases, which contain a full description of the investigational product. A public online registry for gene drive projects has also been proposed *(6, 12)* (Section 5).

Data sharing in public health research is not only expected by major funders of research, but it is widely considered to be an ethical obligation *(45)*. Researchers are strongly encouraged to share field data openly and collaboratively for the greater benefit of the research and disease control communities. Therefore, adequate database platforms should be available for data gathering and storage for evaluation/analysis. Data should be archived in centralized, widely accessible data repositories.[10] Mosquito data should not only include sequence information, but also extensive meta-data describing the type of mosquito (GMM, GDMM, or wild), source of collection, and experimental study design. Data quality and completeness are essential to support modelling efforts, which have an important role to play in each step of the testing pathway for gene drive mosquitoes. As data systems are being designed for field trials, it is recommended that they be developed following established standards where available, such as the Clinical Data Interchange Standards Consortium (CDISC) guidelines *(46)*, in order to develop the data ontology relevant to mosquito vectors and related information. Knowledge translation activities should go beyond data sharing to include knowledge dissemination within both the scientific and host communities.

Policies and mechanisms for inter-project coordination and broader data and information sharing are a necessity. This level of cooperation is best driven by research funders, as exemplified by prior data sharing agreements. Recognizing the importance of transparency for public confidence and future development of gene drive technology, it is recommended that funders work cooperatively on the early establishment of policies for the appropriate sharing of data from GMM research *(7)*. Researchers, funders, policy-makers and government authorities will need to consider whether currently available sites for publicly disclosing relevant information (e.g., the Biosafety Clearing-House [BCH] of the Convention on Biological Diversity [CBD] https://bch.cbd.int/, various clinical trial and nucleic acid databases, and national regulatory agency websites) are sufficient for gene drive technology or whether additional reporting mechanisms are necessary (Section 5). It is important, however, to control or restrict disclosure of data that could result in harm to the research team or host communities, for example, the revelation of facilities or trial sites that could be adversely targeted and stigmatized. Information privacy protections should also be observed for identifiable persons, and for groups where appropriate.

Coordination across projects and programmes, particularly for gene drive technology, is encouraged. Formation of networks among funders, researchers, regulators and policy-makers could encourage information sharing and cooperation in areas of mutual interest and overall importance to the field. The African Union has called for a model of co-development for gene drives for malaria elimination in Africa *(47)*, and the importance of knowledge engagement with expert local publics and scientists has been recognized *(15)*. Coordination of communication strategies among teams working on similar technologies or different approaches, and/or working in the same region is desirable and would contribute to research advancement by enabling better community, stakeholder and public understanding. Such coordination should be encouraged by

[10] VEuPathDB (https://beta.veupathdb.org/veupathdb.beta/app/#getting-started) and ClinEpiDB (https://clinepidb.org/ce/app/) are examples of databases established for the purposes of such research.

those who are aware of various projects within a region, such as academic institutions, regulators, ethics committees and funders. Regional coordination and cooperation will be essential for the implementation and post-implementation phases of a GMM product, particularly one with a gene drive. Principles of respect, mutual understanding and reciprocity will be key to supporting these interactions.

4.2.6 Communication and outreach

Communication and outreach are distinct from community engagement, but contribute to satisfying similar ethical obligations of transparency, inclusive dialogue, and responsiveness to communities, stakeholders and publics. Good communications materials translated into the appropriate language(s) that explain the technology and the research plan must support engagement efforts at all levels *(48, 49)*. Experienced science communicators, as well as sociologists and linguists, should be engaged to help develop the necessary vocabulary to accurately and understandably convey the technical aspects of the research to each group of stakeholders. Project spokespeople should be identified in Phase 1 and provided with appropriate communication skills. Additional training in conflict management could also prove beneficial. Project communications should be developed in coordination with appropriate authorities, anticipating issues of interest to the community, such as the predicted benefits and risks and RM precautions undertaken (Section 3). Although communications strategies may differ among audiences, the basic details regarding project goals, timelines and implementation must remain consistent for a specific project in order to avoid public misunderstandings or confusion.

Local media outlets, such as radio stations, can be useful for making the community aware of the research and where to obtain more information. Fostering well-informed media is an ongoing communications objective, and therefore it will be important to engage proactively with the media through activities such as informational sessions and tours of the research facilities.

Beginning in Phase 1, researchers should have a plan for interacting with those who do not agree with the conduct of GMM research in their community. Some who disagree may hold deep-seated objections that will limit the pursuit of true dialogue, whereas others may have concerns that can be addressed and will be amenable to engagement. Communications planning should include materials that discuss potentially confusing or controversial issues, as well as a crisis communications plan for rapid dissemination of accurate information and assessment of public opinion. Experience has verified that the lack of good outreach and communications can be devastating for trials of new technologies, e.g., *(50)*. Researchers may be confronted with well-organized dissent, which could originate within or outside the community where the research is being conducted. Stories may be disseminated either through traditional media such as newspapers, television and radio, or through new outlets on the Internet and social media. Ordinary word of mouth can also effectively spread widely shared impressions of research. Execution of a robust, proactive engagement plan may help to mitigate any negative messaging. The most important factor in addressing controversy will be the relationships that have already been built with key stakeholders, including the community, in-country scientists, media, civil society, policy-makers, regulators, and relevant government authorities. In-country champions and supportive voices are best positioned to respond to dissenting opinions from the outside.

4.2.7 Justice and equity

An examination of the lives of people who are impacted by vector-borne diseases reveals background conditions of injustice that facilitate and compound the effects of disease, which in turn can exacerbate existing vulnerabilities *(51)*. The people most affected live in low- and middle-income countries and may face poverty, ill health, gender inequality, lack of access to education, and lack of opportunity. For example, malaria kills primarily children in Africa under the age of 5, and malaria in pregnancy is associated with high maternal and perinatal mortality. Those who survive will struggle with poor outcomes as a result of prematurity and low birthweight, the lingering effects dampening child development and flourishing. Children are doubly vulnerable. They must rely on parents and adult caregivers to protect them from malaria and a future of diminished opportunities. This means that not only must interventions such as ITNs, drugs and vaccines be available (i.e., in adequate supply) and accessible (i.e., affordable and within reach), but also caregivers must provide them (i.e., seek and obtain the interventions). In many countries where malaria is endemic, mothers are the primary caregivers for children, which means that the disease burden is disproportionately borne by women *(12)*. This potentially limits them from work, financial security, and education, and thus perpetuates existing social inequalities. Malaria has been found to be associated with slower economic development *(1, 12, 52)*; not coincidentally, so has the disempowerment of women *(53)*. Infection with the Zika virus, another mosquito-borne pathogen, during pregnancy likewise puts infants at risk for long-term developmental abnormalities that may impede their progress and burden caregivers *(54)*.

In considering the impact of GMMs as a public health intervention, it is important to consider how the strategy might exacerbate or alleviate conditions of injustice (Section 3). For example, is it possible that the modification could inadvertently produce a more capable vector that could easily transmit disease and thereby worsen social conditions for women and children? On the other hand, if a safe and effective GMM substantially reduced or eliminated the target disease(s), it would contribute immeasurably to health and economic prosperity. From a social justice perspective, GDMMs might be an ideal public health equity tool. Their health benefits are accessible and equitably distributed to all inhabitants of a treated area – woman, man and child – and capable of reaching remote rural areas where access to current interventions may be scarce or non-existent *(12)*. Importantly, certain types of GDMMs are durable and sustainable, needing no human effort to obtain *(12)*. Consequently, they are capable of impacting many lives without requiring mass adoption in the marketplace *(44)*.

The specific ways that justice can be realized through the fair distribution of benefits and burdens will vary from place to place. An adequate understanding of this will come from engaging with communities and institutions in the country or countries in which the GMM releases are being planned. Considerations will include identifying the groups that have been most disproportionately affected by conditions of social injustice and unjust distributions of social benefits and burdens in the past, and thinking about how GMM research is likely to change the burdens placed on these people for better or worse.

4.2.8 Remediation and post-trial obligations

Once the decision has been made to field test a particular investigational product, researchers and funders incur a responsibility for the safety of the host community. Those funding GMM trials must

be prepared to commit to continued support for trial and post-trial activities for as long as required by regulators and by ethical obligations to the community hosting the field testing. This will include post-trial monitoring for efficacy as well as for safety to health and the environment (Sections 2 and 3). The precise nature of the obligations, including ancillary obligations[11] *(55)*, will depend on case-specific factors identified in RA. Post-trial obligations are often narrowly conceived of as the participant community's or country's "post-trial access" to the tested intervention once the trial has been completed; however, in some cases, such obligations may be much more expansive and can include helping to arrange clinical care and/or social services, referrals, or provision of alternative interventions to facilitate transition from the trial *(57)*. Researchers should not initiate field releases until adequate funds are secured to carry out their regulatory and ethical obligations, which include any necessary mitigation or remediation and post-trial activities *(8)*. Prior to the start of the trial, researchers, funders and government authorities should work together to reach an understanding on potential liability and remediation measures *(8)* (Section 5). In-country scientists have expressed support for GMMs as a biocontrol tool for disease elimination, provided there are contingency measures available to respond to GMMs if hazards become evident during their release *(58)*.

In addition to responsibilities to the communities and countries that host the research, there could be responsibilities to neighbouring countries in the event that they are harmed by the accidental or intended release of GMMs. International conventions that address the transboundary movement of GMOs (Section 5, Regulatory Frameworks) may provide helpful indicators of the obligations of parties involved in GMM research regarding remediation. From an ethical perspective, the movement of GMMs across borders as a public health intervention creates mutual obligations among neighbouring countries to engage in a respectful consultative process, with the understanding that it is not only the country of GMM release that may face potential harms and enjoy potential benefits.

4.3 A strategy for ethical engagement

Appropriate community and stakeholder engagement will be crucial to the success of GMM research on a number of levels. Engagement is essential to meeting ethical obligations related to consent, transparency, communication and trust-building. When conducted through an open exchange of ideas, engagement can also support knowledge sharing that leads to the development of a better and more acceptable product *(59)*. Funders must therefore be prepared to provide support for ongoing engagement activities as an integral component of the research programme.

A broad strategy for helping research teams to meet ethical responsibilities through the conduct of appropriate and meaningful engagement activities will involve an iterative process of ethical reflection, interaction with the host community, stakeholders and publics, and integration of findings from these activities into the ongoing planning and conduct of research.[12] The composition and extent of these groups will likely change with each successive phase of testing. Arguably, for GDMMs that could theoretically spread across large regions, much of the population of

[11] Ancillary obligations are care obligations that researchers owe to research participants that go beyond what is necessary to implement the study safely and with validity *(56)*.

[12] The NASEM report (2016) *(3)* defines "communities" as those living in or near sites where gene drive organisms will be used, "stakeholders" as those who have direct professional or personal interest in gene drive, and "publics" as those who lack a direct connection but have interests or concerns that may contribute to decision-making.

those regions falls legitimately within the category of stakeholder, regardless of where the trials begin. This highlights the importance of engaging with regional and multinational bodies with the authority to represent transnational stakeholders.

Obligations to these different communities, stakeholders and publics will vary in their ethical significance and may be addressed through a range of activities. The ethics and engagement component of a GMM research programme can be visualized at three levels (Fig. 4.1), each with a set of activities that can support meaningful engagement. The strategy presented here should be interpreted as a description of processes and goals, rather than as a prescriptive formula. However, it is recommended that projects on GMM research include time and resources to ensure that these activities are accommodated.

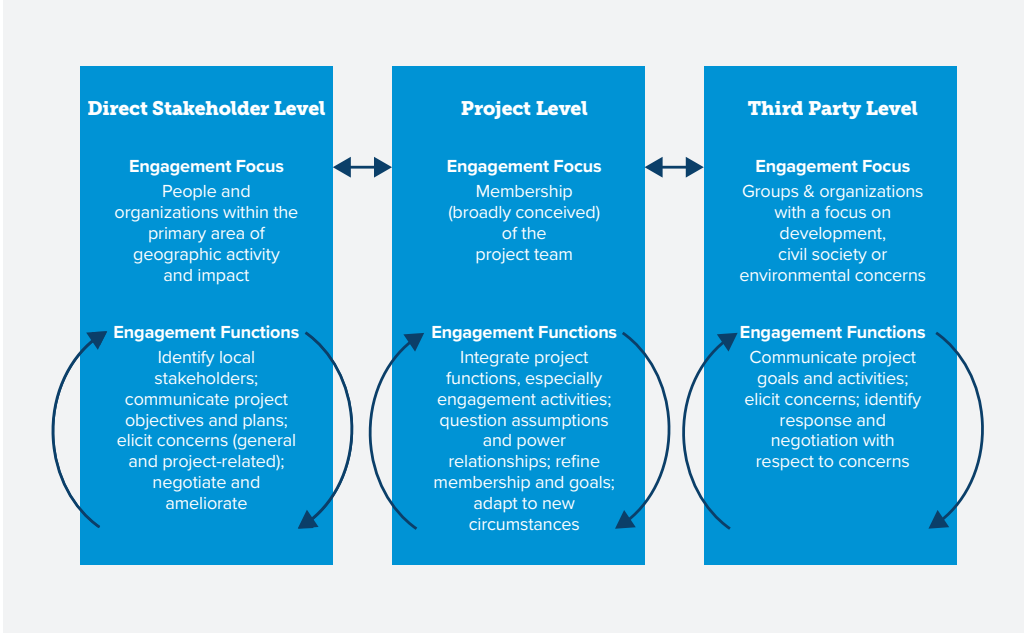
- **At the project level, there are reflective tasks concerning the broader social and ethical issues raised by GMM trials that shape specific management goals and elucidate important learning and evaluation opportunities for the research.** Such tasks are by no means unique to research on GMMs; an explicit recognition and articulation of the ethical purposes of a scientific project is especially useful when the research is likely to attract public interest and scrutiny, as is often the case with any new technology. A systematic analysis that identifies and distinguishes among those who are affected by the research activities through specific interventions or interactions; other members of the host communities who have a stake in the trial; and those who may have legitimate but more distant interests. Determining how to respond to ethical obligations in each case will be a component of the broader ethical reflection needed by the project. An analysis of influential individuals or groups at the different levels will be part of this process. It may be fully appropriate to schedule these activities in conjunction with key project milestones, and it is advised that some form of public reporting about the project and lessons learned be incorporated. Such public reporting might take the form of peer-reviewed publications in appropriate ethics or policy outlets, seminars or workshops, updates on the project website, etc., e.g., *(60–64)*.
- **At the community level, researchers need to anticipate a set of tasks that arise from interactions and effects at the site(s) where field studies are conducted.** Conducting research in host communities brings scientists into direct contact with a number of people, including, but not limited to, those who are classified as human research subjects (Section 4.2.4) or those whose cooperation is necessary for successful completion of research tasks. Additionally, within GMM studies, it is likely that there will be other individuals who do not fall within these categories, but who might still be affected by the conduct of the research. This may include those living near a research project whose daily pursuits and/or livelihoods could be influenced by research activities. People living at the trial site may be in immediate physical contact with the research team, their buildings and vehicles, and with any materials or substances that are released, intentionally or not, into the environment. For GMM research, this includes the perceptions of people who may see, hear or be bitten by any mosquitoes in the field-testing area. There may be some ambiguity in determining who has the potential to be affected in this sense, as there will be movement of both humans and mosquitoes through the locale and complex opportunities for different types of contact. Tasks at the community level overlap with, but are distinct from, regulatory requirements for securing appropriate informed consent and other relevant protections. They may also include involving and empowering local populations in key elements of

research planning and implementation, as well as addressing both real and perceived issues that may arise in connection with the project, including broader socioeconomic impact *(58)*. These tasks collectively operationalize "community engagement".

- **There will be tasks related to the interests of stakeholders and publics, i.e., individuals and groups who are not immediately affected by the research, including civil society organizations (CSOs), the press and the general public.** People living at a distance from the trial may have friends and relatives or even economic interests that they fear could be affected by the conduct of a research project, and, thus, they may also perceive themselves to be affected by it. Moreover, a much larger community of people may take an interest in the conduct or outcome of research, even if they are unlikely to be physically affected by the trial activities themselves. For example, people who are afflicted with a particular disease (along with their friends and family) have an obvious interest in the outcome of research or clinical trials, even if they are not involved with specific trials. Such groups are likely to be strongly supportive of research intended to improve their condition. In a similar vein, people who care about causes such as protecting vulnerable groups or endangered species may take an interest in a wide range of research activities and may not be unilaterally supportive of research goals or procedures. Although the responsibilities to such individuals or groups are quite different from those to communities hosting the trial, it is clear that an effective plan for engaging with a wide spectrum of stakeholders and publics can be critical to the success of research, especially for projects that are expected to attract a significant amount of attention in the press or monitoring from CSOs.

The plan for addressing engagement should include activities appropriate for each level. Each of these activities should be understood as iterative, to be sustained throughout the entire research period, as illustrated by the feedback arrow loops in Fig. 4.1. Each group of tasks should

Fig. 4.1. Levels of engagement focus and function



be understood as an ongoing component of the research activity, and the research plan should include a programmatic discussion of how tasks in each of these three areas will be carried out by members of the research team on an ongoing basis throughout all phases of the testing pathway. Researchers must also take into account that communities, stakeholders and publics may become engaged with each other independent of the project. In addition, consideration must be given to mechanisms to monitor for and avoid stakeholder fatigue over the course of lengthy trials.

One helpful way to use the three levels of activities for planning purposes is to focus on who will need to be involved in completing them. Activities at all three levels of engagement involve members of the research team and will almost certainly involve other staff from the sponsoring organizations as well. Meeting ethical responsibilities to the full range of members in the host community requires a great deal of work on the ground in the local areas encompassing the research field sites. This may not imply contact with literally every individual in the contiguous area, but it must be understood to require appropriate attention to local forms and mechanisms of representation for those who will be affected by the research activities. This may involve negotiation of the environmental and developmental goals, standards, and metrics for the research. For example, directly affected parties and international CSOs alike may have a desire to participate in discussions about how risks to biodiversity are measured or how economic benefits are understood in relation to improvements in public health. One cannot assume that all parties will see any and all forms of economic growth or resource development as beneficial, and investigators should not assume that local communities will always be forthcoming or comfortable with expressing their interests. There may be some areas of overlap between the ethics issues that arise on the ground in interacting with local stakeholders, and the ethics of environment and development that represent the concerns of publics. Some stakeholders and publics might decide to represent the interests of local people, but the local communities may or may not view such representation as legitimate. Anticipating and preparing responses to the issues that are likely to arise in such interactions is an example of something that falls into the category of "broader ethical concerns" to be addressed at the project level.

Activities at all three levels will include the following:

- *Ongoing literature and methodology development* – Whether it be adhering to best practices for clinical and epidemiological research, or engaging with communities, CSOs or the press, there is a body of relevant literature that should be taken into account in the planning and implementation of a project of the scale required for GMM trials. Appropriate review and application of this information will require, at the project level, participation of team members or consultants with the necessary background and expertise.
- *Task planning and implementation* – Based on this literature, those responsible for the ethics and engagement activities will undertake the planning and implementation of project procedures. This may involve staff training, consultations, development of information about the project (including language and culturally appropriate information for use in interacting with residents at field sites), surveys, educational activities, workshops, negotiations, etc.
- *Documentation and reporting* – Record-keeping requirements are specified with respect to research involving human subjects in the context of GCP (Section 5.3.4). However, it must be stressed that other ethics and engagement activities conducted within the project should also be documented to enable later reporting. Mechanisms should be developed to accomplish this. Records of ethical deliberations, as well as stakeholder interactions and agreements

could prove important in the case that challenges to the project arise. Reporting in the form of peer-reviewed articles on the ethics and engagement activities will enrich the literature and help with the planning of future GMM research.

- *Evaluation* – Both internal and external evaluations of how well tasks are being performed at each of the above three levels should be part of the plan. One or more members of the project team could potentially do internal evaluations, but the plan should specify such responsibility explicitly. External evaluators can be drawn from specialists in the ethical dimensions of public health.
- *Iteration* – Evaluation should inform further development and planning. This process will be repeated periodically as needed.

4.4 A tailored, early, sustained engagement process

Before releases begin, researchers, in collaboration with the government authorities of countries participating in the trial, funders and other advisors, should create a tailored plan for achieving effective engagement with communities, stakeholders and publics, so that the opinions of various groups can be considered in the decision-making process over the course of the project. To this end, it will be important to conduct a systematic analysis of influential stakeholders at different levels *(65)*.

At the early stages of research, in addition to in-country members of the project team and community members, researchers should seek to learn from other in-country and/or regional experts and organizations familiar with the local political, religious, social and cultural structure in order to establish an appropriate engagement strategy *(9)*. Effective engagement is context-specific; because of this, it is best undertaken by people who are locally known and respected and who have deep knowledge and understanding of the local value system and culture *(8, 66)*. It will be important to find out about the kinds of motivations and concerns the community might have, about any past negative engagements, and what the community wants/expects in terms of engagement and consent *(67–69)*. Such information is best obtained through ongoing relationships and/or extended ethnographic work with individuals from different social classes, genders, occupations and social roles. Establishing the necessary relationships will be critical to putting in place an appropriate process of ethical review and engagement, especially in the early stages of testing. These relationships will be unique to each setting in which the GMM trials are conducted *(70, 71)*. In many cases, particularly in more traditional community settings, community leaders may play a central role in introducing the researchers to the community and its social structures *(72)* and in providing various levels of ethical scrutiny and permission *(73)*. Social scientists, ethicists and other experts experienced in engagement should be included in the research team to develop and implement the community and stakeholder engagement plan. All members of the project team, however, will interact with the community on some level as part of their ongoing activities and, therefore, it is crucial to ensure that all team members are informed, able to provide accurate information about the project goals, and thereby capable of meaningful engagement.

Guidance about what constitutes effective community engagement continues to be refined with increasing experience. However, one of the first frameworks for community engagement in global health research was developed specifically for GMM research *(74)*. This is a potentially very useful resource for designing community engagement activities that will support authorization from host

communities for early-stage trials (Box 4.1). This study also addressed the issue of how to define the community for purposes of engagement, citing two principles: 1) the community comprises at least those individuals who share the identified risks associated with the proposed research project; and 2) there may be no pre-existing, established community as envisioned by the researchers, but rather, the relevant community may progressively take form in response to specific aspects of the research and the engagement activities associated with the project *(74)*. Building on this pioneering work, recent studies on community and stakeholder engagement for novel vector control technologies also provide additional useful guidance *(8, 34, 75–77)*.

It is important to understand the different levels of government when planning engagement and to respect the requirements at each level. Researchers should engage early with relevant ethics committees to determine the extent of engagement required in preparing for and conducting field studies, and seek guidance in identifying local leaders and key influencers (religious, community, civil society and media) who should be consulted. Projects should coordinate engagement efforts with existing regulatory processes and authorities that will be involved in deploying the product. Involvement and input by the end users of the technology, which in the case of GMMs is likely to be the national disease control programme and/or ministry of health or equivalent, can substantially facilitate public engagement.

Box 4.1. Points to consider for effective community engagement *(74)*

1. **Follow rigorous site-selection procedures.**
2. **Initiate community engagement activities early.**
3. **Characterize and build knowledge of the community, its diversity and its changing needs.**
4. **Ensure that the purpose and goals of the research are clear to the community.**
5. **Provide information about the research.**
6. **Establish relationships and commitments to build trust with relevant authorities in the community: formal, informal and traditional.**
7. **Understand community perceptions and attitudes about the proposed research.**
8. **Identify, mobilize and develop relevant community assets and capacity.**
9. **Maximize opportunities for stewardship, ownership and shared control by the community.**
10. **Ensure adequate opportunities and respect for dissenting opinions.**
11. **Secure permission/authorization from the community.**
12. **Review, evaluate and, if necessary, modify engagement strategies.**
13. **Ensure appropriate levels of transparency and accountability, as this is important for earning public confidence, ensuring that stakeholder needs are met, encouraging the inter-project coordination necessary for responsible field testing, and minimizing risks to human health and/or the environment.**
14. **Ensure that communications about the technology and product(s) are open and honest, avoiding hyperbole about either benefits or risks, and framing the communication to suit the backgrounds and interests of different audiences.**

Appointing an independent ethics advisory group comprising experts external to the project is recommended. This group could include in-country experts and members of involved communities. It can supplement input from existing community advisory boards, functioning as a distinct entity from institutional or national ethics committees to which researchers must submit their proposed activities for review and approval. The primary function of the project's ethics advisory group is to directly advise the researchers on ethical issues related to the project. This advice could be especially helpful in determining how to anticipate and address controversial or sensitive issues. Mechanisms should be established to enable this group to obtain relevant information on issues such as RA, policy, engagement activities and trial status from the project and other advisors, while ensuring that deliberations within this group remain confidential.

Many of the items considered in Box 4.1 address specific needs for information or activities that will almost certainly need to be supervised by persons with training in appropriate field disciplines in the social sciences. Individuals who are naturally fluent in the local language(s), traditions and customs, and who can translate between the community and the research team, while effectively communicating risk, are rare. Furthermore, such individuals will need to commit a significant amount of time to activities within the local communities, which will require a significant financial commitment from the project. The composition of the research team should reflect the process of engaging with local communities, gathering this information and integrating it into the project's planning and deliberation process. Depending on the competencies of both project staff and locally affected parties, it may be appropriate to include representatives from affected groups within the project's governance mechanisms.

Engagement with stakeholders and publics that are distal to the project, but that may have legitimate interests in the conduct and outcomes of GMM field testing, is ethically and practically desirable. The project team must develop and implement planned activities to consider the interests of these third parties and engage with them in a respectful manner. However, the ethical responsibility to inform and engage with these groups must be balanced against the need to use time and other resources effectively to complete the project's overall goals. Undertaking a process of stakeholder analysis early in the project may be helpful in this regard, by facilitating the identification of the groups most likely to influence the success of the project *(78)*. Relevant stakeholders and publics may include the following groups:

- persons associated with global or regional public health and international development organizations, including governments;
- scientists and members of scientific organizations with disciplinary or transdisciplinary links to research activities associated with field-testing activities, including sciences dedicated to public health and infectious diseases;
- persons and organizations engaged in competing approaches for the control of infectious diseases;
- members of organizations focused on promoting the interests and protecting the rights of poor and/or historically marginalized people;
- members of organizations dedicated to the preservation of endangered species, genetic diversity and threatened ecosystems;
- members of organizations with a history of monitoring the role of the sciences in debates over the use of biotechnology;

- individuals and organizations with ties to national, regional and cultural groups active in the areas where field testing is occurring;
- international organizations such as those within the United Nations system.

Some of these groups and the individuals involved with them may have either formal or relatively well-established ways to express views on GMM projects intended to control disease vectors, and to interact with project staff; others may not. These groups may have information or comments that can materially improve project activities. Their support may contribute to a variety of activities, ranging from securing funding or regulatory approvals to facilitating interactions with other scientists, suppliers, publication outlets and local officials. Strategically motivated interactions with these groups are an inherent part of science *(79, 80)* and should not be regarded with skepticism. In the history of agricultural biotechnology, for example, inadequate engagement with groups who had (or who perceived themselves to have) legitimate interests caused many avoidable misunderstandings and much mistrust *(81)*. What is needed for strategic management is a broadening of the perspective that scientists bring to their research to include an effort to understand and then interact with people holding perspectives on the research project that may initially seem to be unrelated to, or at odds with, those of the scientific team.

Once a public engagement strategy has been launched, there should be opportunities for follow-up activities. These could include provision for the submission of comments and questions, but might also involve more extended interactions. It is crucial that stakeholders and publics invited into engagements of this sort are not made to feel that they are being placated, and that the engagement is simply a stalling tactic with little genuine opportunity for them to have any substantive input *(82)*.

4.4.1 Honest broker approach

The mechanisms for accomplishing successful outreach and engagement are still not well understood. One lesson that is now well established is that this kind of activity should not be conceptualized solely in terms of public education, or of simply informing stakeholders and publics of things that the researchers know about GMMs and vector control. Communications launched with this so-called “deficit model” of public engagement have been shown not only to fail, but also to substantially increase opposition and mistrust *(83–87)*. An alternative is to develop mechanisms of interaction with third parties that are based on what Pielke calls “the honest broker” approach *(88)*. The keys to this approach are to first recognize that third-party interests reflect values-based standpoints that inform the way that a scientific research project is going to be seen as either responding to a problem or contributing to a problem. Second, it is critical to develop communications materials about the project that are framed in response to these values-based perspectives. Putatively “neutral” descriptions of projects may fail to provide information that enables third parties to gain a clear understanding of why the research is relevant to them. If such materials are disseminated to parties that are already suspicious or skeptical of a project, these materials can actually exacerbate feelings of mistrust. Finally, it is important to present a picture of the research that includes both strengths and weaknesses relative to the values perspective that would motivate a third party to take an interest in the project. While such a communications strategy should strive to be complete, it should also be sensitive to the need for concise treatment focusing on the problem at hand. Therefore, as part of the engagement process, projects should include a general communications strategy (Section 4.2.6) that takes Pielke’s approach *(88)* into consideration.

4.4.2 Co-development approach

More recently, there has been a shift in thinking about engagement – from knowledge deficit and even honest broker approaches to strategies based on co-development. Traditional knowledge deficit approaches are often based on the perception that publics fear and/or do not understand new biotechnologies, which tends to result in top-down activities designed to educate publics about the benefits of the technology in order to secure acceptance or consent for a field trial *(15)*. Co-development emphasizes the importance of authentic partnerships with communities and publics, particularly where the product will be developed and implemented *(9, 15)*. In its report on *Gene drives for malaria control and elimination in Africa (47)*, the African Union makes the case for a model of co-development that engages local experts, communities, stakeholders and publics, supporting ownership of the technologies in user communities. To practise co-development, it is important to disentangle knowledge engagement from knowledge deficit types of public engagement and to allow for the collaborative reconfiguration of technology design and implementation with publics *(15)*. As such, the focus is on listening and sharing, and on how diverse types of stakeholders can meaningfully shape the design, development and implementation of the technology. An ethically defensible engagement strategy will incorporate aspects of both the honest broker and co-development approaches.

4.5 Engagement at different testing phases

Research and development teams must be prepared and resourced for involvement in a multitude of engagement activities throughout the GMM testing pathway. It is recommended that projects put in place a community advisory board, liaison or reference group to provide input into research planning, as well as feedback on the level of community satisfaction and whether the project is meeting its engagement goals.

4.5.1 Phase 1 – Laboratory and population cage studies

The complexity of GMM research makes it advisable for researchers to commence the "broader issues" engagement component as early as possible, and certainly before Phase 1 proof-of-concept work has been completed *(89)*. Engagement during contained studies conducted within the laboratory, insectary and/or indoor population cage provides an opportunity to explain project goals and operations, develop a relationship with the community, and initiate a trust-building process. One aspect could be a publication that discusses the ethical rationale behind the proof-of-concept work.

While still working in the laboratory or indoor cage, researchers should consider their obligations to the community in the immediate vicinity of the facility, but should also be planning interactions with the larger public. At this phase, options for the ongoing dissemination of information about the project and discussion with the community could involve establishment of a community liaison group, as well as activities such as "open days" at the research facility where community members can observe the work and speak directly with the researchers.

Because the collection of baseline field data must also begin well before releases are contemplated, the start of field studies will represent another early engagement opportunity. It will be essential to begin community engagement and to obtain community support before starting

baseline studies. Engagement planning must take into account and be respectful of local cultural protocols. Baseline studies at the planned release site will require the presence of a field team in villages at the study site. The field team should be prepared to represent the project and to describe its goals. Engagement at field sites may involve local community inhabitants, for example, for their knowledge of mosquito breeding sites or as collectors. Researchers should consider how community values, interests and concerns can inform the target product profile.

Discussion with key opinion leaders should also begin in Phase 1. This would include consultation with government authorities to understand their needs and requirements for a disease control tool, as this might influence product development. This could, for example, include discussions with the national disease control programme.

Engagement actions prior to and during Phase 1:

- Within the project team and with project advisors, establish ongoing mechanisms for considering the social purpose and public health value of the research, and for responding to changing circumstances.
- Conduct preliminary stakeholder analysis; develop plans for distinguishing among those who will be affected by the research activities through specific interventions or interactions, other members of host communities who have a stake in the trial, and those who may have legitimate but more distant interests at stake; identify the stakeholders and publics most likely to influence the success of the project.
- Develop an engagement plan and an initial communications plan with key messages that explain the project and contingency plans for dealing with controversy. The communications plan should be able to reach stakeholders at various levels.
- Initiate public reporting practices, as through publications, project website, etc., to continue throughout the project.
- Prepare plans for field studies; commence discussions with local scientists and community leaders to collect data for decision-making.
- Consult with government authorities to understand their needs and requirements.
- Ensure adequate funding to support engagement activities.
- Consider appointing an external ethics advisory committee to broaden the project team's perspectives.

4.5.2 Phase 2 – Confined field studies

For confined field studies, it will be important to assess community attitudes towards project goals before finalizing field site selection, as the prevailing viewpoint on new technologies may influence the project's success. Physically confined (semi-field) or ecologically/geographically isolated field studies provide additional opportunities for further engagement with the local community. Before and during semi-field testing, engagement activities will include stakeholders living in the region of the field cage and potential release site(s). While likely led by social scientists, these activities should provide access to the project's technical leadership. Interaction with key opinion leaders will become a critical component of engagement at this point.

Principles of risk communication become relevant at this phase, including development of mechanisms to elicit and incorporate stakeholder views on potential harms and options for RM (Section 3). Projects should ensure that the community has access to information on safety studies that have been performed in Phase 1. Being able to observe research staff working inside the field cage may help to build public confidence in the safety of GMMs. However, researchers will need to explain the concept and goals of cage trials, which largely focus on obtaining information that will optimize planning for field release rather than determining efficacy. The community must be advised of the possibility that escapes from the cage may occur and what will be done if that happens. The potential need for repeated cage studies should also be explained.

Prior to initiating field studies, researchers must engage with the community to identify an appropriate method for obtaining community authorization to conduct the studies. What constitutes authorization will be culturally determined and is best left to the community to decide. However, IECs and/or regulatory authorities will need to approve the community engagement and authorization plan, and sufficient time should be allocated for this process. If studies involving human research participation are conducted at this phase, informed consent and ethical approvals must be obtained *(90)*. If ecologically/geographically isolated releases take place in areas of human habitation, consider the need to ensure standard of care as discussed below.

Engagement actions prior to Phase 2:

- Develop informational materials appropriate for engagement with government officials, partner institutions, local community, and other stakeholders and publics; develop plans for media engagement.
- Engage with relevant ethics committees (e.g., institutional or national) and regulatory bodies.
- Finalize site selection; build knowledge about the host community.
- Conduct more focused assessment of relevant local stakeholders; initiate interactions to build understanding of the project among critical decision-makers.
- Initiate activities to explain the project and elicit community feedback; develop plans for community authorization; enact ongoing mechanisms to report on project status and to understand and respond to community perspectives or concerns.
- Secure community authorization and other necessary institutional and government approvals.
- Develop agreements that make explicit the obligations of each institution with respect to liability and remediation measures.

4.5.3 Phase 3 – Staged open field releases

Small-scale releases

Engagement activities will build on those undertaken in Phase 2. As noted above, relevant ethics committees and regulatory authorities may need to approve the community authorization plan before release, which should be included in the project development timeline. Researchers must continue to observe the requirements of human subjects research as applicable.

For initial small-scale releases, the treatment area is likely to be sufficiently small to allow for intense community engagement through personal interactions. The engagement team should clearly describe the studies to the community members, including explanation of both risks and benefits, seek their perspectives and incorporate these into the risk analysis. Although engagement is best performed by social scientists who are familiar with local culture and are experts in engaging community members, opportunities should continue for the community to meet with project leadership. It is advisable to assess the level of community awareness before requesting authorization for a release.

Researchers should anticipate that ethics committees and/or regulatory authorities will require assurance that the community has access to the standard of care for disease treatment, according to national policy. Obligations may differ according to the disease focus and experimental strategy. Consultation with the national disease control programme is recommended to obtain information on how best to integrate GMM field studies with their activities. For malaria studies, access to long-lasting ITNs is an expected requirement because this represents current best practice. Access to medication is not usually the responsibility of the research project, but it is recommended that researchers work with the health care system to ensure that it is readily available. Therefore, at this testing phase, engagement must have proceeded beyond the local community. Researchers should be engaging with local disease and vector control programmes, both to understand their plans for future vector control campaigns that might impact the results and to begin socializing the technology.

For GMMs, and particularly GDMMs, as area-wide control strategies, an important consideration is what opportunities can be made available for individuals or households at the release site to choose not to participate. For small-scale releases, options for responding to such concerns might include project agreement to avoid releasing in the immediate location of the residence, or, if that is unsatisfactory, releasing within some mutually agreed upon distance from the household, and providing mosquito repellent and/or traps to remove mosquitoes from the household. However, none of these options can guarantee complete lack of exposure to the GMMs. This is a subject for transparent discussion with the community.

It is possible that an outbreak of the targeted disease(s) may occur naturally during testing or follow-up, for example, as a result of rains that support mosquito development. This possibility, along with the anticipated disease management activities, should be discussed with the community in advance of the GMM release. Such an event is expected to trigger a need for intensive community engagement and broader public communication efforts. The risk to the project will be linked to the level of understanding and trust that has been established within the community. Researchers must be prepared to work with the community and respond to its needs. For example, this may involve temporarily halting releases or ensuring that treatment is available in the area where the outbreak has occurred.

Before initial releases, it will be important to reach out to stakeholders and publics who are likely to have influence to discuss the technology and testing plans. This includes relevant policy-makers, who must be kept informed of and involved in the planning of all phases of field testing. Although it may not be possible to win the endorsement of all parties, it remains critical to continuously interact broadly to enhance understanding and avoid misperceptions about the research. Before initiation of the trial, discussions of the release plan through existing regional organizations is advised.

Large-scale releases

Later large-scale releases will involve epidemiological efficacy testing that entails interactions with human participants living in the trial area for the purpose of collecting individually identifiable information and/or specimens. Therefore, these releases must be conducted according to standards for human subjects research. However, not all individuals living in the trial area will meet the criteria for human subject, and thus broad community engagement is a vital aspect of preparing for and conducting this phase of testing. As described for small-scale releases, researchers must ensure access to the appropriate standard of care for all households involved in the trial. This will require engagement and coordination with the national disease control programme in trial planning. Because of the potential for geographical spread of GDMMs, engagement must expand rapidly to the national and applicable multinational levels.

At this larger scale, there will be less opportunity for a personal approach to community engagement and authorization. Planning for the scaling up of community engagement activities should commence well in advance of large-scale trials. Community engagement at this broad scale will be challenging because of the inherent difficulty in replicating across extensive and diverse populations the same kind of high-quality, trusting relationships between researchers and stakeholders that were possible at earlier stages through ongoing personal interactions. For large and multi-site trials, additional mechanisms of public engagement, perhaps including social and mass media, may need to be invoked in order to reach and obtain feedback from a broader community. More emphasis may need to be placed on wide distribution of informational materials, interactions with key opinion leaders and influencers, and mechanisms such as reference or liaison groups to obtain community perspectives *(77, 91)*. Such mechanisms also facilitate the monitoring of public opinion and demonstration of trial acceptance. The engagement plan should provide for ongoing communication with stakeholders about the trial's progress, and media interactions may be helpful in this regard. These communications can be disseminated through an array of media, including radio and television, the Internet, and through presentations at professional or public meetings relevant to key interests (e.g., environment, public health, poverty and development, science policy). Other strategies for engagement with the public could utilize universities, libraries or science museums *(92)*.

There is a higher probability of dissent at the scale of epidemiological efficacy trials. Serious consideration must be given to the extent of meaningful opportunities for individuals or households to decline participation. Whereas some options can be presented, such as not allowing releases or monitoring at the home or place of work and/or not participating as human subjects through the provision of data, it will likely be increasingly difficult to prevent some degree of exposure to GMMs, particularly GDMMs, at this testing stage. Expectations regarding the persistence and spread of the gene drive construct within the local mosquito population must be conveyed realistically during the engagement process. It is recommended that a survey of public understanding of these expectations be undertaken prior to releases.

Government-level championing of the research will be essential before this stage, as this will be fundamental to local acceptability of the trial, as well as to regional interactions. In addition to the government of the host country, researchers must consider neighbouring countries as stakeholders and expand regional interactions. For example, information about the project and the results of prior testing could be presented at regional meetings of health ministers and national malaria control programmes. Relevant regional and international nongovernmental organizations

(NGOs) or CSOs with interests in the targeted disease or in emerging technologies should also be engaged before large-scale releases begin.

Engagement actions prior to staged open field releases:

- Review relevant precedents for trial design and broad-scale community engagement; put plans in place to scale up engagement activities as appropriate.
- Take important ethical considerations into account in the development of the trial protocol, and ensure adequate oversight of human subjects research by the relevant ethics committee(s) and DSMB or other approved monitoring mechanism; obtain all necessary institutional and government approvals.
- Engage with local and regional disease and vector control programmes.
- Develop locally appropriate communications plans for multiple field sites; consider that releases may attract global attention and plan to respond accordingly.

4.5.4 Phase 4 – Implementation and post-implementation

Engagement at the implementation and post-implementation phases will primarily be managed at the national level in the context of broader public health activities. It will be important to convey how follow-on monitoring programmes will be managed (Sections 2 and 3).

During product launch, it will be important for all stakeholders at the national and regional level to work together to make the announcement, including spokespersons from involved government authorities, such as national disease control programmes. Regional coordination and cooperation will be particularly crucial in preparing to implement GDMM products.

Country governments may need to engage with disease-relevant international funding partnerships, national development agencies, and regional development banks to secure the needed financial support for wide-scale implementation and follow-on activities.

Engagement actions during and post-implementation:

- Assist agencies in host countries to develop methods for incorporating the technology into their disease control programmes; ensure access to all information relevant to communication and engagement efforts.
- Assist countries as requested to ensure that funding and mechanisms are in place to meet post-implementation ethical obligations.

4.6 Capacity strengthening for ethical engagement

Collaborative international research should be conducted in a manner that improves local research capacity in low- and middle-income countries *(12)*. There may be a need to train bioethicists, scientists, social scientists and biosafety professionals involved in the project about the unique situations encountered in GMM research (Section 1.7). Likewise, scientists may need additional training on ethical obligations in vector biology research. This is a complex subject, and the internationally accepted standards for clinical research are not always directly or clearly

transferable. Additionally, there may be a need to train institutional and national ethics review committees on the importance and process of ethical review of GMM trials. In both developing and developed countries, ethics review committees often lack vector biologists and awareness of ethical issues in entomological research protocols. Attempts should therefore be made to create awareness of such issues among committee members who are responsible for approving and providing oversight for the planned field studies, and to encourage the committees to seek appropriate expertise when considering GMM research/trials.

Safety is a paramount public interest that is addressed through regulatory and other oversight mechanisms (Section 3 and 5). Therefore, strengthening capabilities in science, ethics, biosafety and regulation is an important aspect of responding to ethical obligations by ensuring that research is conducted responsibly *(7)*. Throughout all phases of research, opportunities to partner, educate and train within the countries where testing and implementation is taking place should be supported. Partnerships with researchers and institutions in the countries where the product will be developed and deployed must be conducted in a spirit of co-ownership and co-development of the technology, and in a manner that will promote and foster leadership by in-country scientists *(8)*.

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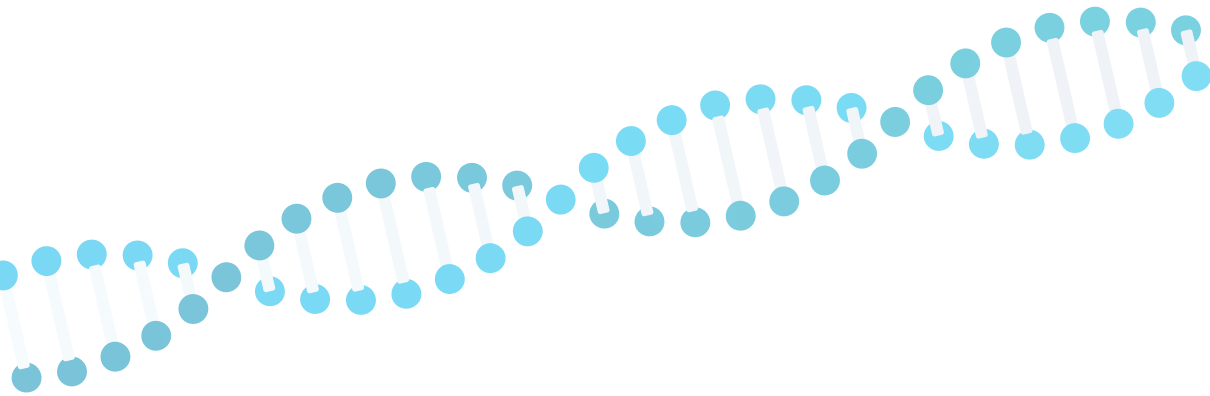

5. Regulatory frameworks

SUMMARY

Development and testing of any investigational GMM product will be controlled through the laws and regulations of a nation, state, province, county and/or lesser levels of jurisdiction. GMO laws in most countries cover all such organisms, even though these were often initially written with GM crops in mind. These laws may need to be adapted or revised, or their implementation modified through regulations, to be appropriate for GMMs and GDMMs. Regulations covering other types of organisms with similar characteristics can inform these adaptations. Depending on the particular country, options and levels exist that may have to be addressed during GMM development, including, but not limited to, requirements of institutional biosafety and ethics committees; laws and regulations governing the development, testing and distribution of public health products, pesticides or biological control agents; laws and regulations pertaining to threatened, endangered and protected species with respect to biodiversity; and laws and regulations specifically pertaining to GMOs. A number of international agreements may also be pertinent to the testing and use of GMMs. The national laws for most GMOs resulted from the implementation of obligations under the Cartagena Protocol for Biosafety (CPB), an agreement under the Convention on Biological Diversity (CBD), to which most countries in the world are parties. While the CPB language only extends to governing transboundary movement, its implementation at the national level has typically resulted in laws and regulations covering research and development activities within a country. An important resource for specific country regulations and contacts relevant to GMMs is the BCH of the CPB.

Regulatory agencies are expected to oversee the testing and use of GMMs. In the case of GMMs for public health use, more than one regulatory agency will likely be involved in official review. Regional agreements will be useful for addressing transboundary movement issues and may also impose oversight obligations.

Regulation is useful both for the scientists involved in GMM development and for the general public, because it provides a defensible a priori mechanism for protecting human health and rights, livestock, economics, and the environment. A reliable, systematic, science-based regulatory process for GMMs that is transparent, without conflict of interest, contains minimal confidential business information, and allows for public engagement and stakeholder input will serve to strengthen public confidence in and acceptance of decisions regarding GMM biotechnologies.

Existing regulatory oversight mechanisms based on laws governing the use of GMOs could be expanded to include aspects of GMM regulation. However, differences between GMMs and other GM technologies must be taken into consideration. In this regard, precedents from the regulation of other technologies, including biocontrol agents and medical products, can be informative.

5.1 The purpose of regulations

Regulations are usually developed from legal interpretations of enacted legislation, laws or acts of a legislative body, and are implemented by government ministries or agencies under the authority of legislation, a law or act. These may be laws and official codes of a nation, state or province, county, municipality, tribe or other jurisdictional unit, and/or laws enacted through provisions of a treaty ratified by participating states. Regulations translate the law into actionable language that, as related to GMMs, provides a process for considering the safety and efficacy of the product.

A regulatory agency (also called regulatory authority, ministry, regulatory body, or regulator) is a public authority or governmental entity responsible for exercising authority over some area of human activity in a supervisory capacity. Regulation of GMMs as public health tools could involve multiple regulatory authorities and require various permits or licenses depending on the phase of research and development or use.

Although risk and benefit assessment, public engagement, and communication are part of the regulatory process, they are not covered in this section, since they are discussed elsewhere in

Key points

- **Existing regulatory frameworks, particularly those dealing with GMOs, medical research, and biocontrol agents, can inform the pathway for GMMs.**
- **In countries that are signatories to the CPB, GMMs are expected to be regulated through a biosafety and/or environmental pathways, but health agencies will play an important and increasing role as testing progresses.**
- **Institutional or national biosafety and ethics committees will be heavily involved in the oversight of GMM research and development.**
- **Regional agreements will be useful to address transboundary movement issues, especially for GDMMs, and may also impose oversight obligations.**

this guidance. RA considers the potential for harms to protection goals, which in the case of GMMs include human and animal health and the environment (Section 3). A benefit assessment for GMMs will derive from their efficacy for vector and vector-borne disease reduction (Sections 1 and 2).

5.2 Local oversight bodies

GMM researchers will interact with a variety of oversight bodies and mechanisms throughout the development pathway (Fig. 5.1). The first level of review of the plans and protocols for research and testing of GMMs is likely to be performed by oversight bodies housed at the involved research institutions.

5.2.1 Biosafety

IBCs are charged by law with the planning and implementation of university and other research facility biosafety programmes for the purpose of protecting the health and safety of all personnel working with potentially hazardous agents *(1, 2)*. While usually affiliated with the research institution performing the work, biosafety committees can also exist at local, provincial, regional, territorial or national levels.

Fig. 5.1. Elements of oversight for GMM research

IBCs may draft institutional biosafety policies and procedures and review individual research proposals for the protection of health and the environment. IBCs will be concerned with all elements of the development pathway of GMMs that are under the institution's control, including shipping, rearing, disposal and export. Concerns relevant to GMMs may relate to the safe handling of recombinant DNA or pathogens perceived to pose a health threat. For example, in the United States of America (USA), IBCs ensure that research conducted at their institution is in compliance with the National Institutes of Health (NIH) *Guidelines for research involving recombinant or synthetic nucleic acid molecules (3)*, and the select agent regulations under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, which authorizes the regulation of the possession, use and transfer of select agents and toxins. The US Federal Select Agent Program (https://www.selectagents.gov/index.html) oversees the possession, use and transfer of select biological agents and toxins that have the potential to pose a severe threat to

public, animal or plant health, or to animal or plant products. This may be relevant to GMMs under certain circumstances because some disease agents transmitted by mosquitoes are considered select agents in the USA; however, *Plasmodium* spp. and dengue virus are not included.

In African institutions, and those in many other countries that are signatories to the CPB, GMM research is likely to be managed under the country's national biosafety authority (NBA), through which an IBC could be constituted. The role of IBCs may vary, but their functions will generally include: preparing applications for contained use activities and referring the applications to the NBA for approval; advising the research institution on matters related to biosafety; assisting their institutions to establish the appropriate monitoring mechanisms for RA and RM; ensuring that the conditions stipulated in the approval are adhered to; reviewing and ascertaining the suitability of both physical and biological containment and control procedures appropriate to the level of assessed risk involved in research, development and application activities; and advising their relevant institutions and principal investigators on mitigation measures to be undertaken in case of an accident *(4)*.

5.2.2 Human participants

In research, regulations on human participation in research generally apply when data will be obtained from individuals through an intervention or interaction, or when personally identifiable information will be made available. This will be the case for some, but not all, aspects of GMM testing (Section 4.2.4). For example, in GMM trials, human subjects regulations would apply to the collection of blood specimens to measure epidemiological endpoints (an intervention) or personal opinion surveys to understand concerns about the research (an interaction).

IECs, also known as institutional review boards or ethical review boards, provide oversight for biomedical and behavioural research involving humans, with the aim to protect the rights and welfare of research participants *(5)*. One role of IECs is to attempt to ensure that human participants in a clinical study understand the facts, implications and consequences of their participation. Informed consent is the mechanism usually used for this purpose. As related to clinical studies, informed consent is intended to be a process of communication between an individual who is contemplating taking part in a study or trial and the physician or scientist who is administering the study. This communication informs the individual's decision about whether or not to participate. The most important aspect of informed consent is voluntary agreement. In order to give informed consent, the individual concerned must have adequate reasoning faculties and be in possession of the relevant facts at the time of consent. Countries will vary with respect to the laws and regulations governing the standards for informed consent required under common law and statutory authorities. The components of informed consent have been delineated in many venues *(6)*.

For aspects of GMM field studies not falling under the definition of human subjects research, mechanisms of community engagement and community authorization (Section 4.2.4) are recommended in order to communicate the goals and risks of the project and determine whether the community agrees to the studies. The community engagement plan should be part of the research protocol reviewed by the IEC.

5.3 Relevant regulation and regulatory precedents

Aspects of existing legislation may be pertinent to or informative for the regulation of GMMs.

5.3.1 Mosquito pests

The intent or purpose of introducing genetic traits for suppressing mosquito populations could possibly be considered and regulated under the definition of a biopesticide, when a pesticide is defined as any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest, as under the US Federal Insecticide and Rodenticide Act definition. In the USA, products intended to reduce the population of mosquitoes (for example, by killing them at some point in their life cycle or by interfering with their reproduction or development), including GMMs to be used for population suppression, are currently regulated as pesticide products by the US Environmental Protection Agency *(7)*.

Mosquitoes can be livestock pests as well as human pests. As with existing legislation for crop pests and diseases, many countries have developed legislation to prevent and control outbreaks of livestock pests and diseases, as these issues affect the economic interests of most countries. Legislation pertaining to mosquito control exists in many countries, mainly for the purpose of enforcing control programme requirements, such as the elimination of larval habitats by citizens.

5.3.2 GM animals

In countries that are signatories to the CPB, GMMs and GDMMs are likely to be regulated from a biosafety perspective (Section 5.3.3), as they meet the definition of a "living modified organism" (LMO), described in the protocol as any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology.

Some countries that are not CPB signatories have adopted a product-based regulatory process. For example, in the USA, whereas GMMs for population suppression are regulated as pesticides by the Environmental Protection Agency, products intended to reduce the pathogen load within mosquitoes or prevent mosquito-borne disease in humans, such as GMMs to be used for population replacement, are currently regulated by the Food and Drug Administration *(7)*.

5.3.3 Environmental protection

Many countries have enacted legislation regulated by environmental and/or fish and wildlife management agencies for the protection of certain species against adverse effects from human activities. Legislation also exists to protect species that have become threatened or endangered due to human action that could result in potential extinction. In cases where other regulatory agencies do not have authority because the nature of a GMO may not clearly fit within their regulatory scope, environmental agencies may have regulatory purview because of the potential for adverse impacts on protected species and species diversity in the environment. In this same regard, regulation by other agencies may require endangered and threatened species impact analysis to be carried out as part of their regulatory process, as is presently required in some countries, including the USA. The CBD and the CPB (Annex 1) are examples of treaties or covenants applying to GMOs that are based on the protection of species biodiversity. GMMs are capable of autonomous or human-facilitated transboundary movement, a subject of the CPB, and this may invoke the regulatory processes of adjacent countries (Section 5.3.6).

5.3.4 Medical research

Regulations dealing with medical research must be considered for GMMs intended to prevent transmission of human diseases. Medical research is guided and governed by a number of ethical codes, treaties, covenants, laws and regulations. Human subjects regulations were developed in response to notorious abuses carried out in the past in the name of research *(8)*. The Declaration of Helsinki is a statement of ethical principles for medical research developed by the World Medical Association *(9)*. The Declaration maintains, among other general principles, that medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights, and should be conducted in a manner that minimizes possible harm to the environment. The Declaration is not a legally binding instrument in international law, but instead draws its authority from the degree to which it has been codified in, or has influenced, national or regional legislation and regulations. In the USA, for example, the National Research Act (Pub. L. 93-348) created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was charged with creating guidelines for ensuring that biomedical research is conducted according to basic ethical principles *(10)*. The International Covenant on Civil and Political Rights (ICCPR) *(11)* is a multilateral treaty adopted by the United Nations General Assembly in 1966 and implemented in 1976. It commits its parties to respecting the civil and political rights of individuals, including the rights to life and self-determination. The ICCPR is part of the International Bill of Human Rights, along with the Universal Declaration of Human Rights and the International Covenant on Economic, Social and Cultural Rights.

Oversight and regulation of the testing and marketing of health care products, including post-marketing surveillance, is conducted by national regulatory agencies.[13] The International Council for Harmonisation (ICH) has established a comprehensive set of guidelines as standards for ensuring the quality, safety and efficacy of pharmaceuticals, including those for GCP *(12)*. The ICH Guidelines are intended to provide a unified standard for regulatory authorities with jurisdiction over medicinal products that are participating in ICH in order to facilitate the mutual acceptance of clinical data by the regulatory authorities in those jurisdictions. These guidelines can be implemented according to applicable national, regional or local rules *(13)*. WHO has developed Guidelines for Good Clinical Practice *(14)* to support countries that have no regulations for clinical trials or whose regulations require supplementation. The African Union is supporting a regional approach for strengthening regulatory capacity and reducing registration times in order to improve access to medicines in Africa *(15)*.

5.3.5 Biological control

In the case of GMMs employing genetic sterility techniques, analogies to the experience of biological control (biocontrol) using irradiated vectors may be informative *(16)*. For systems involving fertile GMMs, and especially GDMMs, classical biocontrol that uses living organisms to control insect pest populations may be more analogous. Typically, biocontrol agents are natural enemies of the pest species, e.g., living predators or pathogens. Once these organisms are released into the environment, there is little opportunity to recall or eliminate them, and autonomous transboundary movement is possible. The International Plant Protection Convention (IPPC) *(17)* describes the responsibilities of governments and importers of exotic classical biological control agents. It encourages governments to adopt specific legislation and regulations, and

[13] A partial list is available at https://globaledge.msu.edu/industries/healthcare/regulatory-agencies.

designate an authority to administer such activities. Furthermore, it recommends that both hazard identification and exposure analysis of risks should be carried out following International Standards for Phytosanitary Measures (ISPMs) *(18)*. Many countries have established mechanisms for RA and the regulation of biocontrol agents. In general, the regulation of biocontrol agents involves national agricultural and/or environmental authorities. Some countries require analyses of risks and benefits, and decisions are made on this basis (e.g., New Zealand, Kenya); others (e.g., Australia) do not consider benefits to be part of the standard regulatory process because the target status of the pest has already been accepted *(19, 20)*.

5.3.6 Transboundary movement

Transboundary regulatory issues may apply to GMMs because mosquitoes are mobile and therefore potentially able to spread to unintended areas with permissive environments. This possibility will increase with the scale of the release and/or with the presence of gene drive systems that are designed and intended to spread throughout an ecozone. RA and RM plans should take into account the possibility that GMMs, and especially GDMMs, may disperse autonomously across political borders into suitable habitats that are contiguous, or even into regions separated by geographical or biological barriers due to human travel and transport. If it is known or expected that introduced traits will move across national borders, then the need for multilateral regulatory approval by countries not separated by species barriers and therefore subject to introduction of the GMMs should be thoroughly considered. To engage in a multilateral regulatory process may involve international agreements or country approvals prior to introduction into one country within a contiguous ecozone. International or multinational organizations will be best suited to provide leadership in a regional regulatory process for implementing GMMs intended to spread widely (see Annex 1 for further discussion).

Within international conventions that address the transboundary movement of GMOs or exotic agents, and that therefore may apply to GMMs, there is general consensus that, prior to release into the environment or implementation, there should at least be a notification, as specified in the CPB, but preferably also a bilateral or multilateral consultative process with other countries to which the GMMs may move. With respect to GMMs that are disease vectors, this could be within the context of a collaborative process to control the vector. Relevant conventions that address transboundary movement include the following:

- The World Trade Organization (WTO) Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement), Articles 3, 5 and 6 *(21)*;
- The CBD, Articles 3, 4, 5, 14 and 17;
- The CPB;
- The IPPC, Article 7 (International Cooperation) and IPPC ISPM Nos. 3 and 11 *(18)*;
- The UN Convention on Environmental Impact Assessment in a Transboundary Context *(22)*;
- Code of Conduct for the Import and Release of Exotic Biological Control Agents *(23)*;
- The ASEAN Agreement on the Conservation of Nature and Natural Resources, Article 3 *(24)*;
- The Convention of Conservation of Nature in the South Pacific, Article V;

- The Convention for the Conservation of Biodiversity and the Protection of Wilderness Areas in Central America, Article 24;
- The International Health Regulations, as amended, 1983 *(25)*.

Countries that are parties to such conventions must develop their own regulations to implement the requirements. For countries that are parties but without laws or regulations, the CPB describes an Advance Informed Agreement process that would apply prior to the first intentional transboundary movement of GMMs intended for environmental release in the receiving country (Article 7, paragraph 1). An example of how this provision has been implemented in Europe is found under Regulation (EC) No 1946/2003 of 15 July 2003 *(26)*. This regulation aims to set up a common system for notifying and exchanging information on the transboundary movements of GMOs to third countries. The ultimate goal is to ensure that movements of GMOs that may have adverse effects on the sustainable use of biological diversity and on human health take due account of the environment and health. The Advanced Informed Agreement procedure is specific to the first intentional introduction to the environment and does not include contained use if undertaken in accordance with the standards of the Party or non-Party of import. Implementation of the CPB in national legislation would supersede the Advanced Informed Agreement provisions.

The most relevant examples of multilateral collaborative transboundary efforts come from the field of biocontrol. One such success was the introduction of the parasitic wasp, *Epidinocarsis lopezi*, of the cassava mealybug, *Phenacoccus manihoti*, in Africa *(27)*. The parasite was released in more than 50 sites, and by the end of 1986, it was established with good results in 16 countries. National introductions were facilitated by inputs from international organizations to guarantee the safety and efficacy of the introductions. These organizations included the International Institute of Tropical Agriculture (IITA), the International Institute of Biological Control (IIBC) and the African Union's Inter-African Phytosanitary Council (IAPSC). The IAPSC did not make blanket decisions for member countries, and releases were national decisions once imported into quarantine. The IIBC's main concern was to ensure that the wasp was free from disease and hyperparasites, while the IITA assisted governments with the local production, release and monitoring of parasites. The IITA also coordinated a large capacity-building element in the programme, which helped to create a generation of technical experts across Africa with knowledge of both biocontrol and quarantine. Another example of a successful regional programme has been the biological control of the hibiscus mealybug, *Maconellicoccus hirsutus* Green, in the Caribbean *(28)*.

Examples of regional control programmes for human disease include the Pan African Tsetse and Trypanosomiasis Eradication Campaign *(29)* and the Onchocerciasis Control Programme *(30)*, both of which contain vector control components. The International Atomic Energy Agency supports regional programmes to implement radiation-based SIT for the management of major insect pests, including mosquitoes *(31)*. The African Medicines Agency *(32)* is a specialized agency of the African Union established to enhance the capacity of State Parties and Regional Economic Communities (RECs) to regulate medical products. The Agency works to coordinate and harmonize regulatory systems in the region in order to improve access to quality, safe and efficacious medical products on the continent. The African Union Development Agency–New Partnership for Africa's Development has also initiated a regional vector management programme to promote a multisectoral approach in building the regulatory capacity to evaluate genetically based vector control applications *(33)*.

5.3.7 Dual or hostile use

Some have raised concerns about the potential for dual use of gene editing technologies, including gene drive, suggesting that research on these technologies has the potential for both beneficial breakthroughs and damaging misuses *(34)*. Management of dual use research of concern in the life sciences has been discussed in a number of venues, with principles, guidelines and policies developed, e.g., *(35–37)*.

The Biological and Toxin Weapons Convention *(38)* applies to "microbial or other biological agents, or toxins... that have no justification for prophylactic, protective or other peaceful purposes" or are designed to be used for hostile purposes or armed conflict. Both the Biological and Toxin Weapons Convention and the UN Security Council Resolution 1540 (2004) *(39)*, which deals with biological weapons intended for terrorist purposes, have been interpreted as prohibiting the use of gene drives to push harmful genes into a population *(40)*. Likewise, the Environmental Modification Convention *(41)* prohibits military or other hostile use of environmental modification techniques that have widespread, long-lasting or severe effects. Because the GMMs and GDMMs described in this guidance are expressly developed for use in national disease control programmes to improve public health by reducing the transmission of mosquito-borne diseases, there is no direct relevance of these conventions.

5.4 Other guidance and recommendations

Recommendations, guidance and policies relevant to the RA and regulation of GMMs and GDMMs have been developed over decades. Although they may not be backed by force of law, these documents provide important context for developers and other stakeholders (see Table 5.1). These documents generally fall into the category of soft governance (guidance from regional or international bodies) or national governance (issued by authorized agencies) *(42)*.

Table 5.1. Chronological listing of some national and international regulatory and biosafety developments relevant to RA and testing of GMMs, including GDMMs

Year	Development	Relevance	Website
2000	Cartagena Protocol on Biosafety to the International Convention on Biological Diversity	Established Biosafety Clearing-House for information on national biosafety regulations and contacts	http://bch.cbd.int/
2000-2004	WHO-TDR technical consultations on GM vectors	Began the process of defining requirements for testing and implementation of GM vectors	http://www.sciencemag.org/content/298/5591/119.full
2005	IPPC Guidelines for the Export, Shipment, Import and Release of Biological Control Agents and Other Beneficial Organisms	IPPC-approved international standards for RM related to guidance for regulation of new biotechnologies related to crop pests and human disease vectors	http://www.fao.org/3/a-j5365e.pdf

Year	Development	Relevance	Website
2007	North American Plant Protection Organization (NAPPO) Guidelines for Importation and Confined Field Release of Transgenic Arthropods in NAPPO Member Countries	NAPPO-approved regional standard to provide guidance in the use of transgenic arthropods while protecting plant health (archived)	https://nappo.org/application/files/4115/8404/3736/RSPM_27_ARCHIVED-EN.pdf
2008–2011	WHO-TDR Training Manual on Biosafety for Human Health and the Environment in the Context of the Potential Use of Genetically Modified Mosquitoes	Training manual used for a series of capacity-strengthening courses for researchers, policy-makers, regulators, etc. aimed at developing countries for decision-making on regulatory frameworks, biosafety, RA, and ethical, social and cultural issues related to the use of GM vectors	https://tdr.who.int/publications/i/item/2015-07-20-biosafety-for-human-health-and-the-environment-in-the-context-of-the-potential-use-of-genetically-modified-mosquitoes-gmms-
2009	United States Department of Agriculture (USDA) Environmental Impact Statement on Use of Genetically Engineered Fruit Fly and Pink Bollworm in APHIS Plant Pest Control Programs	USDA Animal and Plant Health Inspection Service (APHIS), in cooperation with several states and foreign countries, provides a full RA of genetically engineered fruit fly species and pink bollworm for use in various applications of a GM SIT	http://www.aphis.usda.gov/plant_health/ea/downloads/eis-gen-pbw-ff.pdf
2009	WHO-TDR and FNIH-sponsored Technical Consultation on Progress and Prospects for the Use of Genetically Modified Mosquitoes to Inhibit Disease Transmission	Reviewed current status and requirements for future development of GMMs for malaria and dengue control; initiated development of a guidance framework for the evaluation of GMMs including quality standards for assessing safety, efficacy, and ethical, social and cultural considerations	https://tdr.who.int/publications/i/item/progress-and-prospects-for-the-use-of-genetically-modified-mosquitoes-to-inhibit-disease-transmission
2013	European Food Safety Authority (EFSA) Guidance on the Environmental Risk Assessment of Genetically Modified Animals	Guidance for the environmental RA of genetically modified animals, including insects, fish, birds and mammals, to be placed on the EU market	http://www.efsa.europa.eu/en/efsajournal/pub/3200.htm
2014	WHO Guidance Framework for Testing of Genetically Modified Mosquitoes	WHO guidance on the development pathway for GMMs, including considerations for efficacy and safety testing, ethics, engagement, and regulatory precedents	https://tdr.who.int/publications/i/item/2014-06-26-the-guidance-framework-for-testing-genetically-modified-mosquitoes
2015	Science and Technology Committee of the UK Parliament Report on Genetically Modified Insects	Recommendation on potential applications of GM insects for commercialization, regulation and public engagement	https://publications.parliament.uk/pa/ld201516/ldselect/ldsctech/68/6802.htm

Year	Development	Relevance	Website
2016	Guidance on Risk Assessment of Living Modified Organisms and Monitoring in the Context of Risk Assessment	CBD-created guidance on RA for GMOs to supplement Annex III of the Cartagena Protocol, with a special section on living modified mosquitoes (submitted for approval at the Cartagena Protocol COP-MOP8, but not formally endorsed as the only guidance that could be used by Parties)	https://www.cbd.int/doc/meetings/bs/mop-08/official/bs-mop-08-08-add1-en.pdf
2017	Scientific Opinion of the French High Council for Biotechnology on Use of Genetically Modified Mosquitoes for Vector Control	Report on the benefits and limitations of the use of GMMs in France, with considerations for RA criteria	http://www.hautconseildes-biotechnologies.fr/en/avis/avis-relatif-a-lutilisation-moustiques-gm-dans-cadre-lutte-antivectorielle
2017	Report of the Royal Society Te Aparangi Gene Editing Panel on Use of Gene Editing to Create Gene Drives for Pest Control in New Zealand	Report on the rationale, international and regulatory considerations for use of gene drive-modified organisms to control several invasive species in New Zealand	https://royalsociety.org.nz/assets/Uploads/Gene-editing-in-pest-control-technical-paper.pdf
2017	Synthetic Gene Drives in Australia: Implications of Emerging Technologies	Report of the Australian Academy of Science considering the benefits and hazards of synthetic gene drives in an Australian context, with considerations for containment, RA, and public engagement	https://www.science.org.au/support/analysis/reports/synthetic-gene-drives-australia-implications-emerging-technologies
2017	Report of the Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology, Montreal, Canada, 9 December 2017; CBD/ SYNBIO/ AHTEG/2017/1/3	The AHTEG concluded that organisms containing engineered gene drives fell under the definition of an LMO as per the Cartagena Protocol.	https://www.cbd.int/doc/c/aa10/9160/6c3fcedf265dbee686715016/ synbio-ahteg-2017-01-03-en.pdf
2017	European Academies Scientific Advisory Council Policy Report 31: Genome Editing: Scientific Opportunities, Public Interests and Policy Options in the European Union	Reviews applications of gene editing in a range of organisms, including gene drive applications where it supports recommendations of the 2016 report from the US National Academies of Science, Engineering and Medicine	https://easac.eu/fileadmin/PDF_s/reports_statements/Genome_Editing/EASAC_Report_31_on_Genome_Editing.pdf
2017	Statement of the Norwegian Biotechnology Advisory Board on Gene Drives	Reviews risks and benefits of gene drive technologies and provides recommendations for further research	https://www.bioteknologiradet.no/english/

Year	Development	Relevance	Website
2017	Decision of the African Union: Assembly/AU/Dec.649 (XXIX) at the 29th Ordinary Sitting in Addis Ababa	Commits to sustain the gains made in the fight against malaria and monitor antimalarial drug resistance and insecticide resistance; further commits to invest in the development and regulation of the gene drive technology; and requests the African Union Commission, WHO and NEPAD Agency to support these initiatives.	https://au.int/sites/default/files/decisions/37294-assembly_au_dec_642_-_664_xxix_e_1.pdf
2018	Netherlands Commission on Genetic Modification Report on Experiences with Gene Drive Systems that may Inform an Environmental Risk Assessment (CGM 2018-03)	Reviews status of research on gene drive-modified organisms, with considerations for RA	https://cogem.net/app/uploads/2019/07/CGM-2018-03-Report-Gene-Drives-met-kaft1.pdf
2018	National Institute for Public Health and the Environment RIVM Letter report 2018-0090 Risk Assessment Method for Activities Involving Organisms with a Gene Drive under Contained Use	Provided recommendations specifically tailored to the system in the Netherlands for authorizing research with gene drive-modified organisms under contained use	https://www.rivm.nl/bibliotheek/rapporten/2018-0090.pdf
2018	Report of the High Level African Union Panel on Emerging Technologies (APET) on Gene Drives for Malaria Control and Elimination in Africa	Report on the relevance of gene drive technology for malaria in Africa, with recommendations for development, regulation, public engagement and capacity strengthening	https://www.nepad.org/publication/gene-drives-malaria-control-and-elimination-africa
2018	National Biosafety Technical Commission of Brazil (CTNBio) Normative Resolution No. 16 of January 15, 2018	Updates Law 11.105 to consider new precision breeding innovation techniques, including gene drive	http://bch.cbd.int/database/record.shtml?documentid=113509
2018	Statement of The Royal Society, UK, on Gene Drive Research: Why It Matters	Considers several important questions about gene drive technologies, and recommends continued research	https://royalsociety.org/~/media/policy/Publications/2018/08-11-18-gene-drive-statement.pdf
2019	Office of Gene Technology Regulator, Department of Health, Australian Government, Guidance for IBCs: Regulatory Requirements for Contained Research with GMOs Containing Engineered Gene Drives	Provides guidance to IBCs and researchers on the regulatory requirements for physical confinement and licensing of contained research on GMOs with engineered gene drives	http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/53139D205A98A3B-3CA257D4F00811F97/$File/Guidance%20on%20gene%20drives.pdf

Year	Development	Relevance	Website
2019	International Union for the Conservation of Nature Report on Genetic Frontiers for Conservation: An Assessment of Synthetic Biology and Biodiversity Conservation	Considers governance frameworks for synthetic biology and biodiversity conservation, including biodiversity implications of synthetic biology applications not intended for conservation benefit, such as gene drive approaches for malaria suppression in Africa	https://portals.iucn.org/library/efiles/documents/2019-012-En.pdf
2020	Environment Agency Austria Report on Gene Drive Organisms: Implications for the Environment and Nature Conservation	Provides an overview of the technical status of gene drive technologies and their proposed applications, and provides recommendations for technology assessment	https://ensser.org/wp-content/plugins/download-attachments/includes/download.php?id=rdBfKqri8S8SG3S-fl_3AYUPmgS4Xv3cK82saU-WlpHng,
2020	Guidance Framework for Testing the Sterile Insect Technique as a Vector Control Tool against *Aedes*-Borne Diseases	Guidance issued by the International Atomic Energy Agency and WHO on requirements for the testing and deployment of the SIT	https://www.iaea.org/sites/default/files/aedes-who-iaea-2020.pdf
2020	Report of the Ad Hoc Technical Expert Group on Risk Assessment, Montreal, Canada, 15 April 2020, CBD/CP/RA/AHTEG/2020/1/5	Reaffirmed that LMOs containing engineered gene drives fall within the scope of the CPB, and provided considerations for RA	https://www.cbd.int/doc/c/a763/e248/4fa326e03e3c126b9615e95d/cp-ra-ahteg-2020-01-05-en.pdf
2020	Swiss Academies Fact Sheet Gene Drives: Benefits, Risks and Possible Applications	Report from the Swiss Academy of Sciences containing recommendations for technical assessment and ethical considerations	https://scnat.ch/en/uuid/i/045a3073-e301-5215-a0a0-3ca3d5b85a78-Gene_drives%3A_benefits%2C_risks%2C_and_possible_applications
2020	EFSA	Adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterization, environmental RA and post-marketing environmental monitoring of GM insects containing engineered gene drives	https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2020.6297

5.5 Regulation at different testing phases

Oversight at multiple levels will be required at all testing phases. Different regulatory precedents will be informative for addressing different issues along the GMM development pathway. Precedents from the RA and regulation of biocontrol agents will be relevant to decision-making about moving from indoor contained testing to the first field release. Precedents from the regulation of GM crops will be informative for the conduct of initial confined and small-scale field testing. Large-scale field testing for epidemiological impact will have elements in common with clinical trials for other public health tools.

GMM developers should begin engaging transparently with regulatory authorities as early as possible in order to provide information on the technology and understand all regulatory requirements that must be met. Plans for testing, monitoring and any additional necessary RM activities should be agreed upon by developers/responsible institutions and regulators prior to the initiation of each study, with clear assignment and acceptance of responsibilities. This should include discussion of liability issues and remediation requirements (Annex 1).

5.5.1 Phase 1 – Laboratory and population cage studies

Work in this phase will be conducted in physical confinement, with indoor laboratories, insectaries or population cages, ensuring efficacy and safety testing under appropriate containment conditions and operating procedures. Certification of physical containment facilities may be required *(43)*. Permits for movement between containment facilities will be required for importation and interstate/international/interregional movement. Inspections may be conducted to assess the security of containment according to the established guidelines and regulatory requirements. IBCs will be involved at the beginning of this stage.

Other regulatory requirements could be for permits to rear mosquitoes and for permission to work with human disease vectors (and the disease agents, if applicable) in the regulatory jurisdictions where the research is to be conducted. Provisions for surveillance and monitoring for escaped GMMs will likely be part of the regulatory requirements in Phase 1 because of possible containment failures. Plans for managing the risk of escape of transgenic mosquitoes are expected to be a required element of regulatory applications for physically confined testing. These plans should include emergency control or mitigation measures for escaped GMMs through proven means, such as pesticide applications. International biotechnology product movement permits and quarantine systems have already been established in many countries for the movement of living plant and animal agents that are transgenic.

Containment guidelines have been published *(44)*, recommending Arthropod Containment Level 2 for transgenic arthropods. Considerations for physical confinement of GDMMs will differ according to the gene drive system and depending on whether or not the laboratory is in a location where the GDMM species is native. Some have recommended that all laboratory experiments involving gene drive systems should use at least two stringent confinement strategies, including molecular, ecological, reproductive and barrier methods *(45)*. The ecological option – conducting experiments in locations where mosquitoes cannot establish – may not be available to researchers in disease-endemic countries. Others recommend confinement of GDMMs capable of spreading in the environment at an "enhanced Arthropod Containment Level 2"; this refers to mosquito containment measures equivalent to Arthropod Containment Level 3 but without Level 3 pathogen containment requirements *(46, 47)* (Section 3.8.1).

Compliance with international standards for quality assurance of data should be implemented (e.g., development of and compliance with SOPs, and strict documentation and record keeping); however, Good Laboratory Practices certification has not been considered necessary *(47)*. In some countries, a licence or authorization may be required to work with gene drive-modified organisms in containment *(48, 49)*.

Due to the risk of local establishment of the modification resulting from accidental escape of low numbers of non-localizing, self-sustaining GDMMs from physical confinement, in cases where

appropriate containment facilities and well-trained staff are not available within the endemic area country, or risk of escape from containment cannot be brought to acceptable levels for other reasons, then initial safety work with driving constructs should be performed outside of a region suitable for establishment, but in mosquitoes of the genetic background from the area where they will be field tested (the ecological confinement option). Scientists from the endemic area partner institutions should be involved in the development that takes place outside the region. As is the case with conventional biocontrol agents, emphasis must be placed on the safety evaluation of GDMMs in containment before the initiation of field releases (Section 3).

5.5.2 Phases 2 and 3 – Confined and open field testing

Developers who expect their GMM product to undergo policy recommendation development by WHO are advised to consult with the WHO Vector Control Advisory Group (https://www.who.int/groups/vector-control-advisory-group) on study design prior to finalization of field testing plans *(50)*.

Regulation of physically or ecologically/geographically isolated field studies of GMMs in Phase 2 will require the conduct of RA or other similar environmental assessment to supply scientific rationale and evidence that risk to the environment or human and animal health will be kept to acceptable levels through the confinement methods (Section 3). Under current regulatory expectations based on the testing of GM crops, contact between the GMO and the general population is expected to be minimized. However, for mosquito species that feed almost exclusively on people, field testing is likely to take place in areas of human habitation. Researchers must consult with regulatory authorities to ensure understanding of the biological basis for this requirement. Provisions for surveillance and monitoring are expected to be part of the regulatory requirements in this phase. Regulation will also likely require a plan for emergency control or mitigation measures (Section 3).

Researchers must also be transparent with regulators about the potential for transboundary spread of the GMMs or gene drive construct at any stage of field testing. This should be based on all available data and information, including predictions obtained from modelling. The decision to move to field testing is a particularly critical step in the pathway for GDMMs because of the increased potential for spread of the gene drive construct in a hospitable environment, including spread across national borders. This is especially the case for those with self-sustaining, non-localizing drive systems (Section 3). External all-hazard RAs conducted by qualified third parties with no vested interest in the product are recommended for these GDMMs. These RAs should be made public by developers as a means of informing stakeholders and building confidence in the rigour of the study (Section 3). Such external RAs are not expected to replace those conducted by, or required for submission to, regulatory agencies, which will be guided by national protection goals and scope as circumscribed by regulations, but can inform trial planning and regulatory applications.

Requirements for semi-field or outdoor cage testing, which could be an intermediate stage between indoor contained studies and field releases, may vary between national regulatory authorities. This situation is complicated for self-sustaining, non-localizing GDMMs because of the potential for local establishment of the transgenic construct resulting from the escape of only a few individuals (Section 3). For these GDMMs, if there is a distinction between regulations governing contained use and those related to field trials, it is advisable to request permission for both semi-field testing and small-scale release in the same application in order to accommodate

the possibility of unintended escape from the cages. Because applications for both types of study will require information about the field site, the regulatory application process may be simplified if semi-field testing and the initial field release are conducted in the same location. Researchers must notify the responsible regulatory authority of any breach of the specified confinement requirements. Under the CPB, the decision to notify or consult with neighbouring country regulators will be made by the regulatory authority of the country in which the study is conducted.

Regulatory requirements for open releases will be commensurately more stringent than for confined studies. Open releases of GMMs will entail regulatory determination that they will not introduce genetic changes into indigenous wild populations of vectors that may result in unacceptable risks to health or the environment (Section 3). As in previous phases, regulatory authorities will likely require appropriate control measures to be available in order to mitigate or remediate any adverse effects in case the GMMs fail to perform as expected.

For GDMMs, it may be desirable to leave a release site active after achieving the primary efficacy endpoint to allow for longer term monitoring of efficacy and safety. The concept of leaving the release active may require a change in regulatory paradigms, and this might be informed by precedents from the regulation of biocontrol agents. The scientific case for leaving the release site active for long-term follow-up should be made early in the regulatory process in order to enable discussion of the need and process for such follow-up.

5.5.3 Regional cooperation

Prior to Phase 2, regional coordination should be encouraged among countries where further field testing is planned in order to provide regulatory authorities in those countries with the opportunity for input into protocol development, RA, testing requirements, risk mitigation and data collection methods. This engagement may minimize expectations for confined testing to be repeated in each country. Regional scientific cooperation and a framework for regional regulatory assent or authorization will become increasingly important as field releases increase in scale and scope. When transboundary movement to adjacent countries or states with separate regulatory jurisdiction is expected or intended, the regulatory requirements of the countries or states into which the GMMs may move also need to be addressed (Section 5.3.6). RA and/or IA for field testing may require consideration of the potential effects on neighbouring countries.

While other possible mechanisms exist (Section 5.3.6), establishing a regional cooperative framework would provide a useful means to coordinate communication among countries on issues such as the notification of field releases, post-implementation monitoring, and the response to unintentional transboundary movement. Moreover, it is possible that releases of more than one GMM product could be conducted in the same or nearby locations. This could introduce additional considerations for RA, efficacy and safety assessment, and stakeholder engagement, especially if the different GDMMs might spread and spatially overlap, perhaps resulting in regional differences in their effect. If multiple studies were to take place within the same country, the national regulatory authority would be responsible for determining how to address such management requirements. However, this situation could present a management challenge if the different studies were being regulated by different neighbouring countries. A regional coordination process would also be helpful in this context.

5.5.4 Phase 4 – Implementation and post-implementation

Many factors will influence a decision to implement GMMs at scale, including evidence for efficacy and safety, as well as proof of acceptability, deliverability and sustainability (Sections 1.6 and 1.7). Countries that look to WHO for guidance should be aware of the process for evaluation and recommendation of vector control products *(50)*. Post-implementation surveillance, when required, should be intended, designed and executed to detect movement and introgression of the genetic construct within vector populations, ongoing efficacy, and any unintended changes in vector biology that may result in adverse effects on health or the environment (Sections 2 and 3). There is currently no uniform precedent from either biocontrol or GM crops that provides a means to predict what regulatory requirements for monitoring might be imposed by regulatory agencies for GMMs, including GDMMs. It is assumed that throughout the development pathway, GMMs will have undergone extensive and recurring RAs, as well as rigorous study during the field trial phase, which should have included studies of health and ecosystem effects. If there had been any indication of unacceptable adverse effects that could not be suitably mitigated, or if it had been determined that those adverse effects were not outweighed by the benefits, the product should not have proceeded to this stage. While the studies conducted throughout the development pathway might provide sufficient data and experience to justify a decision that post-release surveillance is not necessary, post-approval monitoring is widely accepted for other public health tools and some level of ongoing safety monitoring, such as for effects on a relevant subset of NTOs, may be a regulatory expectation for GMMs (Section 3.8.4). However, if post-implementation monitoring is required, parties should agree on what is to be monitored, to what extent, how, by whom, and how the data will be collected and analysed. Responsibilities should also be made clear for the response should an adverse event be detected, including who would be expected to respond.

5.6 Additional considerations pertinent to GMM regulation

5.6.1 Field site selection

When considering the site for field trials, countries where there is an established national biosafety law or other relevant legislation and regulations should be prioritized. There should also be a functional regulatory infrastructure to properly oversee compliance with legal requirements. Laws pertaining to liability and redress for personal injury or environmental damage (including damage to biodiversity), as well as damage to socioeconomic or ethical concerns are also in place in many countries, some of which assign strict liability to specific entities such as the inventor, patent holder, or developer, among others (Annex 2). While these considerations are relevant even at the contained use phase, the move to field testing increases the exposure to liability. Trial insurance will be an important consideration in this regard.

Where there is the potential for transboundary movement, the possibility for regional regulatory cooperation among pertinent countries should be explored in the process of site selection. Regional bodies relevant to the potential field site could be consulted to determine their understanding of and interest in the use of GMMs for disease prevention, as well as to gauge their ability to assist with the coordination of informational and regulatory activities in countries neighbouring the one where the studies will occur.

5.6.2 Public consultation

Regulatory decision-making should include opportunities for public consultation (Sections 3 and 4). In many cases, this is mandated within the national regulatory process. For example, in the USA, agencies are required to make efforts to provide for public involvement in their processes under the National Environmental Policy Act (NEPA) *(51)*. This principle is also applied in certain multinational agreements. The CPB specifies that Parties shall promote and facilitate public awareness, education and participation, and ensure that the public has access to information on GMOs that may be imported. Furthermore, Parties shall, in accordance with their respective laws and regulations, consult the public in the decision-making process. Likewise, the United Nations Economic Commission for Europe (UNECE) Convention on Access to Information, Public Participation in Decision-Making and Access to Justice in Environmental Matters *(52)* establishes a number of rights of the public (individuals and their associations) with respect to transparency, consultation and access to justice.

Decision-makers must be able to weigh all the evidence that they receive in terms of relevance and quality. An example is provided in the *WHO Handbook for guideline development (53)*, which takes into account factors such as the comprehensiveness of the materials, the method by which risk of bias was assessed, the methods by which the data were collected and presented, and the similarity to results from different studies.

5.6.3 Registries

Trials for the epidemiological efficacy of GMMs are effectively clinical trials and, as such, should be registered according to internationally agreed upon standards *(54)*. WHO *(55)* and many national governments maintain clinical trial registries *(56)*.

The BCH (https://bch.cbd.int/) established under the CPB provides a means for Parties to exchange information relating to regulatory decisions concerning GMOs, as well as a variety of scientific, technical, environmental and legal information that can contribute to building the regulatory capacity. Decisions on importation or releases of GMOs are mentioned specifically as an item that the BCH is to make publicly available. The decisions that Parties record on the BCH include not only those that are planned and authorized by their respective regulatory agencies, but also, in compliance with Article 17 of the CPB, any occurrence (not necessarily authorized) under its jurisdiction resulting in a release that leads, or may lead, to an unintentional transboundary movement that might have an adverse effect on biodiversity.

WHO maintains a central database that collects information on clinical trials using human genome editing technologies *(57)*. Although this particular database is not applicable to GMMs, a similar centrally managed trial registration or declaration website could provide a useful tool for facilitating regional oversight, as well as public transparency *(40, 47, 58)*.

5.6.4 Litigation

Regulation by litigation may occur when the regulation does not have sufficient basis in law or is perceived to be procedurally flawed, such as with RA that does not meet international and refereed publication standards or legally required administrative procedures, or when lingering

public concerns are thought to be inadequately resolved by a functioning regulatory system. Litigation or lawsuits, court injunctions, court orders, fines and penalties may then drive the regulatory process. While part of the democratic process, this would be an undesirable regulatory outcome for GMMs that could result in the loss or delay of beneficial public health innovation, as well as loss of public confidence.

5.6.5 Capacity strengthening

The building of regulatory capacity to evaluate GMMs will be unequivocally important. In some countries, there will be a need to train members of IBCs or national regulatory authorities on issues relevant to the review of GMM studies. Some institutions may have yet to establish an IBC, in which case this would be a prerequisite before research could begin. Although many developing countries have enacted national biosafety legislation, others still lack a regulatory framework to deal with GMOs. Even if legislation is present, there may not be a functional system in place to regulate GMMs. If experience with RA and the regulation of GMOs exists, GM plants or crops may provide the only precedent. Because most legislation dealing with GMOs assigns regulatory responsibility to a separate national biosafety authority, and because the focus of those authorities will probably have been on GM crops, those bodies will consist of members who have limited knowledge or experience with the technologies involved in producing GMMs or how to regulate them. Regulatory paradigms evolving from experience with multinational GM plant or crop corporations may result in high costs and extended indecision on regulatory approvals. The national regulatory authority for health care products should be involved in decision-making about GMMs, particularly in the progression to field testing. However, health regulators may operate within a pharmacy or medical background with experience in regulating drugs, vaccines and devices. Background information will be required for agencies that are unfamiliar with vector control tools.

It will be critical to begin working with regulators very early in the GMM development pathway in order to identify the appropriate regulatory agencies and initiate proactive, scientifically relevant and science-based communications that will build understanding about the GMM technology, and the goals and methodologies of the research and investigational product. There may be a need for additional training in vector biology procedures and/or biosafety in order to ensure that decision-makers are empowered to competently assess plans for GMM trials and reach definitive and defensible conclusions that are aligned with the enforcing regulations. These needs must be anticipated, and means to address them must be identified and budgeted for accordingly.

Mechanisms for regional cooperation in decision-making will be needed to address transboundary movement concerns for GMMs, and there will be capacity strengthening needs associated with such mechanisms. This is illustrated by the stepwise programme under development by the African Union–New Partnership for Africa's Development, which aims to establish robust regulatory systems for GMMs in support of a continental vector control programme *(33)*.

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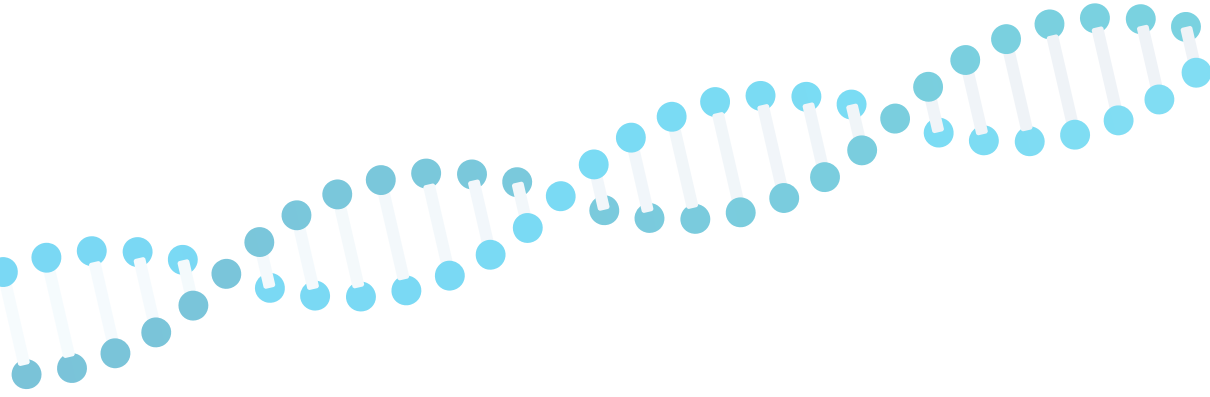

Annexes

Annex 1. Additional information on relevant international organizations, treaties and covenants

World Trade Organization (WTO)

Agreements and public health: a joint study by WHO and the WTO Secretariat (1): This study explains how WTO Agreements relate to different aspects of health policies. It covers several areas, including infectious disease control, environment and biotechnology. The study explains that countries have the right to take measures to restrict imports or exports of products when necessary to protect the health of humans, animals or plants. If necessary, governments may put aside WTO commitments in order to protect human life. The study discusses the application of biotechnology to foods and potential health effects such as gene transfer from plants to microbial or mammalian cells, transfer of antibiotic resistance, and allergenic effects.

The WTO Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) *(2)* articles include, but are not limited to, the following, which also pertain to autonomous transboundary movement of genetically modified mosquitoes (GMMs):

Article 1, General provisions – This Agreement applies to all sanitary and phytosanitary measures, which may, directly or indirectly, affect international trade. A sanitary or phytosanitary measure is any measure applied to protect animal or plant life or health within the territory of a member from risks arising from the entry, establishment or spread of pests, diseases, disease-carrying organisms, or disease-causing organisms.

Article 2, Basic rights and obligations – Members have the right to take sanitary and phytosanitary measures necessary for the protection of human, animal or plant life and health.

Article 3, Harmonization – To harmonize sanitary and phytosanitary measures on as wide a basis as possible, members shall base their sanitary or phytosanitary measures on international standards, guidelines or recommendations. Members shall play a full part, within the limits of their resources, in the relevant international organizations and their subsidiary bodies, in particular the Codex Alimentarius Commission, the International Office of Epizootics, and the international and regional organizations operating within the framework of the International Plant Protection Convention (IPPC), to promote the development and periodic review of standards, guidelines and recommendations with respect to all aspects of sanitary and phytosanitary measures.

Article 5, Assessment of Risk and Determination of the Appropriate Level of Sanitary or Phytosanitary Protection – Members shall ensure that their sanitary or phytosanitary measures are based on an assessment, as appropriate to the circumstances, of the risks to human, animal or plant life and health, taking into account risk assessment techniques developed by the relevant international organizations. In the assessment of risks, members shall take into account available scientific evidence; relevant processes and production methods; relevant inspection, sampling and

testing methods; prevalence of specific diseases or pests; existence of pest- or disease-free areas; relevant ecological and environmental conditions; and quarantine or other treatment.

Article 6, Adaptation to Regional Conditions, Including Pest- or Disease-Free Areas and Areas of Low Pest or Disease Prevalence – Members shall ensure that their sanitary or phytosanitary measures are adapted to the sanitary or phytosanitary characteristics of the area, whether all of a country, part of a country, or all or parts of several countries from which the product originated and to which the product is destined.

Article 12, Administration – A Committee on Sanitary and Phytosanitary Measures is hereby established to provide a regular forum for consultations. It shall carry out the functions necessary to implement the provisions of this Agreement and the furtherance of its objectives, in particular with respect to harmonization.

Annex B Section 3 of The SPS Agreement, recognizes standards developed by the IPPC and the World Organisation for Animal Health that apply to living modified organisms (LMOs) in respect to the following:

- protection of human or animal life from risks arising from additives, contaminants, toxins or disease-causing organisms in food, beverages and feedstuffs;
- protection of human life from plant- or animal-carried diseases (zoonoses);
- protection of animal or plant life from pests, diseases or disease-causing organisms; and
- protection of a country from damage caused by the entry, establishment or spread of pests.

Regulations on GMMs should conform to the provisions of this Agreement, such as scientific risk assessment and least trade-restrictive measures.

The WTO Agreement on Technical Barriers to Trade (TBT) *(3)* allows governments to take appropriate measures if they have a legitimate objective, such as protecting health or the environment.

The Convention on Biological Diversity (CBD)

Since the adoption of the Convention, the Conference of the Parties (COP) has initiated national action plans in over 193 countries and raised biodiversity awareness, leading to the adoption of the Cartagena Protocol on Biosafety (CPB). Mechanisms for implementing the CBD consist of National Biodiversity Strategies and Action Plans (NBSAPs) *(4)*. The articles of the CBD that may pertain to the transboundary movement of GMMs include the following:

Article 3, Principle – States have the sovereign right to exploit their own resources pursuant to their own environmental policies and the responsibility to ensure that activities within their jurisdiction do not cause damage to the environment of other states or of areas beyond the limits of national jurisdiction.

Article 4, Jurisdictional Scope – The Convention applies to each contracting party, regardless of whether the effects of their activities occur within or beyond the area of their national jurisdiction.

Article 5, Cooperation – Each party shall, as far as possible and as appropriate, cooperate with other contracting parties, directly or through competent international organizations in respect of areas beyond national jurisdiction.

Article 8, In-situ Conservation – Each party shall establish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms, which are likely to have adverse environmental impacts, taking into account the risks to human health.

Article 14, Impact Assessment and Minimizing Adverse Impacts – Each party shall introduce appropriate procedures requiring environmental impact assessment of its proposed projects that are likely to have significant adverse effects and allow for public participation. Each party shall promote – on the basis of reciprocity, notification, exchange of information, and consultation – bilateral, regional or multilateral arrangements within the area under jurisdiction of other states. Each party shall notify immediately affected states of danger or damage.

Article 17, Exchange of Information – The contracting parties shall facilitate the exchange of information from all publicly available sources relevant to the conservation and sustainable use of biological diversity, taking into account the special needs of developing countries.

The CBD, through its Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA), organizes Ad Hoc Technical Expert Groups (AHTEGs) to develop opinions and reports on issues that will be considered by the COP to the Convention. An AHTEG on Synthetic Biology has been formed by the SBSTTA. Decision XIII/17 of the Conference of the Parties to the Convention on Biological Diversity *(5)* took note of the conclusion of the AHTEG that living organisms developed through synthetic biology are similar to LMOs as defined in the CPB. The COP noted that the general principles and methodologies for risk assessment under the CPB and existing biosafety frameworks provide a good basis for risk assessment of living organisms developed through synthetic biology, but such methodologies might need to be updated and adapted.

Subsequently, the AHTEG on Synthetic Biology has concluded:

> "[M]ost living organisms already developed or currently under research and development through techniques of synthetic biology, including organisms containing engineered gene drives, fell under the definition of LMOs as per the Cartagena Protocol" *(6)*.

The term "LMO" includes GMMs and gene drive-modified mosquitoes (GDMMs). The validity of this conclusion was affirmed by the AHTEG two years later *(7)*. Therefore, these decisions and conclusions identify not only GMMs but also GDMMs as organisms that are subject to the CPB under the CBD.

The CPB is the most significant internationally ratified treaty to influence regulation of GMMs in developing countries. It is a supplementary agreement to the CBD and is an international treaty governing the movements of LMOs. It entered into force in September 2003 when the number of signatory countries reached 50. It now includes at least 172 nations, including most developing countries. The CPB affirms the precautionary approach contained in Principle 15 of the Rio Declaration on Environment and Development *(8)* and Annex II of the Deliberate Release Directive of the European Economic Community *(9)*, requiring regulators to consider all potential risks, even when there is scientific uncertainty around their extent or existence. Principle 15 of the Declaration states the following: "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation" *(10)*.

This precautionary principle or approach is analysed in the published European Commission of the European Communities *Communication on the precautionary principle (11)*. EU codifications of the precautionary principle are further described in the *Summaries of EU legislation (12)*. In the precautionary principle or approach, if an action or policy has a suspected risk of causing harm to the public or to the environment, in the absence of scientific consensus that the action or policy is harmful, the burden of proof that it is not harmful falls on those taking the action. This principle allows policy-makers to make discretionary decisions in situations where there is the possibility of harm from taking a particular course or making a certain decision when extensive scientific knowledge on the matter is lacking. The principle implies that there is a social responsibility to protect the public from exposure to harm when scientific investigation has found a plausible risk, but interpretation has been extended by some to mean that regulatory approvals should not be granted until all possible or theoretical risk and safety issues have been scientifically resolved, regardless of societal needs and potential benefits.

A significant provision of CPB Article 21 is the establishment of the Biosafety Clearing-House (BCH) (https://bch.cbd.int/) for the compilation and international exchange of important information on the movement and release of GM organisms. This useful database contains information relevant to LMOs and national legislation, with some governments having provided their biosafety regulatory frameworks and other pertinent regulatory information including important contacts. The purpose of the BCH is to (a) facilitate the exchange of scientific, technical, environmental and legal information on and experience with LMOs; and (b) assist parties to implement the CPB.

The Biosafety Information Resource Centre (BIRC; http://bch.cbd.int/database/resources/) is an electronic catalogue of biosafety-related publications and information resources, including news services, e-mail list servers, online databases and search engines, reports and case studies, journals, newsletters, and teaching materials (manuals, toolkits and presentations). Its objective is to increase the accessibility and use of available biosafety information and resources for policy-makers, educators, researchers and the general public.

Whereas national regulations take precedence, aspects of the CPB to be considered for the planning of GMM field trials are outlined below.

Protocol Article 4 – The Protocol applies to the transboundary movement, transit, handling and use of LMOs, taking also into account risks to human health. Under the Protocol, a country that wants to export LMOs for intentional introduction into the environment must seek advance informed agreement from the importing recipient country.

Article 6 – The provisions of this Protocol with respect to the advance informed agreement procedure shall not apply to LMOs in transit and transboundary movement of LMOs destined for contained use. Contained use means any operation, undertaken within a facility, installation or other physical structure, which involves LMOs that are controlled by specific measures that effectively limit their contact with, and their impact on, the external environment.

Article 8 – Pertains to notification and that “The notification shall contain, at a minimum, the information specified in Annex I.”

Article 10 – Concerns decision procedures and that decisions taken by the party of import shall be in accordance with Article 15, which addresses risk assessment.

Article 14 – Concerns bilateral, regional and multilateral agreements and arrangements. "The Parties shall inform each other, through the Biosafety Clearing-House, of any such bilateral, regional and multilateral agreements and arrangements that they have entered into."

Article 17 – Concerns unintentional transboundary movements of LMOs and emergency measures.

Article 19 – Regarding competent national authorities, states "Each Party shall designate one or more competent national authorities, which shall be responsible for performing the administrative functions required by this Protocol and which shall be authorized to act on its behalf with respect to those functions."

Articles 8, 10 and 13 and Annex III – Concerns environmental risk assessment, taking into account human health.

Part II of the *Final report of the Ad Hoc Technical Expert Group on Risk Assessment and Risk Management under the CPB on specific types of LMOs and traits, C. Risk assessment of living modified mosquitoes (13)* addresses the following:

- specific aspects of risk assessment of living modified mosquitoes developed for use in the control of human and zoonotic diseases;
- issues to be considered in the risk assessment, including effects on biological diversity (species, habitats and ecosystems); new or more vigorous pests, especially those that have adverse effects on human health; harm to or loss of other species; and disruption of ecological communities and ecosystem processes;
- gene flow through cross-fertilization; horizontal gene flow; and persistence of the transgene in the environment;
- evolutionary responses (especially in target mosquito vectors or pathogens of humans and animals); and
- risk management strategies.

The CPB has also initiated a process under its established work on risk assessment, pursuant to COP/MOP decision CP-9/13, to determine whether additional risk assessment guidance (supplementary to the above-mentioned overall risk assessment guidance) is necessary for gene drives *(14)*. This process involves another AHTEG (on Risk Assessment). Further information on this process is provided in the following section on reports, studies and initiatives.

The Nagoya–Kuala Lumpur Supplementary Protocol on Liability and Redress to the CPB *(15)* concerns the question of what would happen if the transboundary movement of LMOs caused damage. The negotiators were, however, unable to reach any consensus regarding the details of a liability regime under the Protocol. As a result, an enabling clause to that effect was included in the final text of the Protocol (Article 27), which states:

> "The Conference of the Parties serving as the meeting of the Parties to this Protocol shall, at its first meeting, adopt a process with respect to the appropriate elaboration of international rules and procedures in the field of liability and redress for damage resulting from transboundary movements of living modified organisms, analyzing and taking due account of the ongoing processes in international law on these matters, and shall endeavor to complete this process within four years."

The Supplementary Protocol entered into force on 5 March 2018, the 90th day after the date of deposit of the 40th instrument of ratification, acceptance, approval or accession *(16)*. By the closing date, it had been signed by 51 Parties to the CPB. The binding international agreement creates obligations for states that need to be implemented domestically.

African Union

In February 1999, the African Group in the CBD and the Organization for African Unity (OAU, now the African Union) began to develop the African Model Law (AML) on Safety in Biotechnology. Its first purpose was to provide for a harmonized approach towards biosafety in Africa, serving as a model legal instrument for developing national biosafety legislations. The AML was first developed in 2001, but its contents have been controversial because of the strict nature of its provisions, which apply not only to living genetically engineered organisms (GEOs; i.e., LMOs), but also equally to the products of such organisms. In an attempt to gain greater acceptance of the AML and to use it as a basis for harmonizing the positions of African countries on biosafety, there has been some attempt at revising the AML since 2007.

Despite the general approach of the AML, the report of the African Union High Level African Panel on Emerging Technologies (APET) *(17)* explains that gene drive technology has been identified as a potential new option to augment existing interventions in pursuit of achieving the African Union Agenda 2063. A set of key recommendations are proposed for consideration in the future development and application of the technology. The APET report *(17)* concludes that even though gene drive for malaria elimination is still in its early development phase, it presents realistic options to achieve high-impact, well-organized and large-scale malaria control and elimination. It may take many years before actual products are ready for field deployment, but the potential benefits for African countries against malaria will most likely be extensive. Work is underway to establish a West African Integrated Vector Management to support the harmonization of regulatory requirements in the Economic Community of West African States that will be a model for the continent *(18)*.

International Plant Protection Convention (IPPC)

The IPPC is a multilateral treaty with the purpose of protecting plants and plant health from the introduction and spread of pests of plants, and to promote measures for the control of plant pests. Biological control agents used to control plant pests fall under the scope of the IPPC. The IPPC is identified in the WTO's SPS Agreement *(2)* as the international standard-setting organization for plant health. Both the IPPC and SPS Agreement also affirm the sovereign right of all member nations to take the necessary measures to protect plant life or health from the introduction and spread of pests. Members of the WTO are legally obligated to base their phytosanitary measures on the International Standards for Phytosanitary Measures (ISPMs) developed under the auspices of the IPPC. Like the SPS Agreement and the IPPC, the CPB also requires countries to base measures for LMOs on risk assessment. In June 2000, an open-ended expert working group made up of phytosanitary experts and representatives of the CBD agreed that organisms that do not pose a threat to plant health (e.g., transgenic mosquitoes) do not fall within the scope of the IPPC.

IPPC ISPMs *(19)* contain guidance that may be usefully adopted and incorporated into the national regulation of GMMs, especially pertaining to international movement, release and risk assessment.

- IPPC ISPM No. 2, Framework for Pest Risk Analysis (2009) *(20)* – This standard provides a framework that describes the pest risk analysis (PRA) process within the scope of the IPPC. It introduces the three stages of PRA: initiation, pest risk assessment, and pest risk management.
- IPPC Guidelines for the Export, Shipment, Import, and Release of Biological Control Agents and Other Beneficial Organisms (ISPM No. 3) *(21)* – This standard provides guidelines for risk management related to the export, shipment, import and release of biological control agents and other beneficial organisms. It lists the related responsibilities of contracting parties to the IPPC, National Plant Protection Organizations (NPPOs), or other responsible authorities, importers and exporters. The standard addresses biological control agents capable of self-replication (including predators, parasites, nematodes, phytophagous organisms, and pathogens, such as fungi, bacteria and viruses, as well as sterile insects and other beneficial organisms), and also includes those packaged or formulated as commercial products. Provisions are also included for import for research in quarantine facilities of non-indigenous biological control agents and other beneficial organisms. The scope of this standard does not include LMOs.

The IPPC includes the following provision in relation to the regulation of biological control agents and other beneficial organisms. Article 7*(1)* states:

With the aim of preventing the introduction and/or spread of regulated pests into their territories, contracting parties shall have sovereign authority to regulate, in accordance with applicable international agreements, the entry of plants and plant products and other regulated articles and to this end, may... c) prohibit or restrict the movement of regulated pests into their territories and; d) prohibit or restrict the movement of biological control agents and other organisms of phytosanitary concern claimed to be beneficial into their territories.

- Contracting Parties (member nations) should designate an authority with appropriate competencies to be responsible for export certification and to regulate the import or release of biological control agents and other beneficial organisms. The responsible authority should:
  - carry out pest risk analysis prior to import or release of biological control agents and other beneficial organisms;
  - ensure, when certifying exports, that the regulations of importing countries are complied with;
  - provide and assess documentation as appropriate, relevant to the export, shipment, import or release of biological control agents and other beneficial organisms;
  - ensure that biological control agents and other beneficial organisms are taken either directly to designated quarantine facilities or, if appropriate, passed to mass-rearing facilities or directly released into the environment;
  - ensure that importers and, where appropriate, exporters meet their responsibilities; and
  - consider possible impacts on the environment, such as impacts on non--target invertebrates.

IPPC ISPM No. 11 *(22)* addresses risk analysis for quarantine pests, including analysis of environmental risks and LMOs. The standard provides details for the conduct of PRA to determine if pests are quarantine pests. It describes the integrated processes to be used for risk assessment, as well as the selection of risk management options. Section S2 of ISPM 11 includes guidance on evaluating the

potential phytosanitary risks to plants and plant products posed by LMOs. This guidance does not alter the scope of ISPM 11, but is intended to clarify issues related to the PRA of LMOs.

Food and Agriculture Organization (FAO)

The FAO *Code of conduct for the import and release of exotic biological control agents (23)*: The objectives of this Code are to facilitate the safe import, export and release of exotic biological control agents by introducing internationally acceptable procedures for all public and private entities involved, particularly where national legislation to regulate their use does not exist or is inadequate. The Code describes the shared responsibility of the many segments of society involved and the need for cooperation between importing and exporting countries. Standards are described that encourage responsible and generally accepted trade practices, and assist countries to design regulations to control the suitability and quality of imported exotic biological control agents. They also address the safe handling, assessment and use of such products. Responsibilities are outlined for the entities addressed by this Code, including governments, individually or in regional groupings; international organizations; research institutes; industry, including producers, trade associations and distributors; users; and public--sector organizations such as environmental groups, consumer groups and trade unions.

All references in this Code to a government or governments shall be deemed to apply equally to regional groupings of governments for matters falling within their areas of competence. Governments should designate the competent authority empowered to regulate or otherwise control and, where appropriate, issue permits for the importation and release of biological control agents. The organization should prepare a dossier for submission to the national authority if the organism has already been imported and is currently being held in containment, or if the organism is being imported directly for release. It should include, among other information, a risk assessment to estimate the possible environmental impact in the new area in which any possible risks to animal and human health should be identified. This authority should consult with authorities in neighbouring countries within the same ecological area and with relevant regional organizations to clarify and resolve any potential conflicts of interest that may arise between countries. Where problems (i.e., unexpected deleterious incidents) are identified, the authority is to consider and, where appropriate, ensure corrective action is taken and inform all relevant interested parties.

World Organisation for Animal Health

The World Organisation for Animal Health (OIE; https://www.oie.int/en) was founded in 1924. Some standards developed by the OIE deal with diseases that have human health and biosafety significance. The OIE has had a Working Group on Biotechnology since 1996. The OIE is principally concerned with animal or livestock health issues that may be associated with GM animals and vaccines. Examples of subjects from OIE sources involving biotechnology include:

- regulations governing veterinary medicinal products containing GMOs in the European Community;
- biotechnology applications in animal health and production;
- disease-resistant GM animals;
- DNA vaccines for aquaculture;
- traceability of biotech-derived animals.

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Annex 2. Examples of national legislation and regulation pertaining to GMMs

This annex provides a brief description of the regulatory framework of several countries that have engaged in or contemplated research on genetically modified mosquitoes (GMMs). Additional information on national approaches to gene drive regulation and governance can be found in the *Gene drives: pursuing opportunities, minimizing risks* report from Johns Hopkins University *(1)*.

The most important resource for specific country GMM regulations and contacts is the Cartagena Protocol on Biosafety (CPB) Biosafety Clearing-House (BCH; https://bch.cbd.int/). Another source of information is the Convention of Biological Diversity (CBD) Biosafety Information Resource Centre (BIRC; http://bch.cbd.int/database/resources/). The regulatory status of genetically modified organisms (GMOs) in some countries, and particularly GMMs, is dynamic, and various ministries or agencies within a country might choose to exercise regulatory authority over a particular GMO, GMM or activity involving them, depending upon the case.

Brazil

In Brazil, Federal Law No. 11105/2005 *(2)* is the principal legal framework for biotechnology. It provides safety regulation and inspection tools for activities concerning GMOs and their by-products. This law, created the National Biosafety Council (CNBS), provided a new format for the National Biosafety Technical Commission (CTNBio; http://ctnbio.mctic.gov.br/inicio) and established a framework through the National Biosafety Policy (PNB). The CNBS is linked directly to the Office of the President of Brazil and is responsible for providing the PNB. The CNBS is responsible for establishing principles and guidelines for the administration of federal agencies that regulate biotechnology. The CNBS also analyses the socioeconomic impact of the commercial use of GMOs and their by-products, and issues the final approval of licenses and policies, when deemed necessary.

Products derived from precision breeding innovations (PBI; such as gene editing) in many cases may not contain transgenes and, therefore, are not included in the category of GMOs in the Brazilian biotechnology law. Normative Resolution no. 16 regulates the assessment exemption by CTNBio and provides for a case-by-case approach.

This resolution lists eight possible results of the application of PBI. In addition, in its annex 1, the resolution exemplifies nine techniques considered to be PBI, without excluding others that may be used to generate PBI products in the near future. The text accommodates an assessment exemption for products not formally listed. In addition, the resolution indicates paths for the risk assessment of organisms with gene drives. In its annex 2, the penultimate item establishes: “if the product uses the gene drive principle, which may allow the conferred phenotypic change to have the potential to spread throughout the population of the recipient organism, care must be taken to monitor the organism, using at least two different strategies”.

CTNBio belongs to the Ministry of Science and Technology of the Federal Government of Brazil and is a consulting and deliberating multidisciplinary body that provides technical assistance to

support biotechnology decisions at the federal level. CTNBio is responsible for approving research and development of GMOs under specific conditions and approving tests or commercialization of any biotechnology product for human, animal and plant use. The Commission has 27 members that include scientists with biotechnology backgrounds, federal officers, lawyers and other experts.

All organizations (university, research institution, and industry) must have an internal biosafety commission (CIBio) that is responsible for ensuring biosafety within their areas. Any activity in containment using risk class 1 GMOs is assessed and eventually authorized by the CIBio, and an annual report is sent to CTNBio. For all other risk classes or for activities in confinement (field releases), the CIBio assesses the proposal, but CTNBio gives the final approval. Annual reports are also the rule. Research labs and other facilities dealing with GMOs must get a Certificate in Biosafety (CQB), given by CTNBio.

The requirements for approval of commercial products are strict and acceptance may take years. However, new rules have been established that reduce the burden on some products and expedite their commercialization. These approvals mainly involve new plant varieties, but has also included mosquitoes, yeasts and viruses. After approval, the executing organization is required to monitor for adverse effects if the pre-approval risk assessment identifies a risk.

The Brazilian regulatory framework has been applied to GMMs *(3)* and Brazil has approved the use of GMMs *(4)*. These GMMs do not contain a gene drive construct; they express a conditional lethal gene and a fluorescent marker. An example risk assessment is available through the BCH *(5)*.

Burkina Faso

Burkina Faso signed the CPB in May 2000 and ratified it in August 2003. This action laid the foundation for the establishment of a National Biosafety Committee and the government's adoption of the Biosafety Guidelines for Biotechnology in 2004. A National Biosafety Agency was established in 2005, and finally the first Biosafety Law *(6)* was passed in 2006. Current biosafety regulation is conducted under a revised law *(7)* that was passed in 2012. The law provides for a National Biosecurity Agency (Agence Nationale de Biosécurité, ANB), as well as two consultative bodies: the National Biosecurity Observatory (Observatoire National de Biosécurité, ONB) and the National Biosecurity Scientific Committee (Comité Scientifique National de Biosécurité, CNSB).

The ANB is the national competent authority for all GMO activities in Burkina Faso and is housed in the Ministry of Research and Scientific Innovation (Ministère de la Recherche Scientifique et de l'Innovation, MRSI). It is responsible for the following:

- ensuring the enforcement of the national regulations on GMOs and products derived from them;
- ensuring the security of the development and use, including the cross-border movement, of any GMOs and their derived products, except those developed for pharmaceutical use;
- reviewing and authorizing applications for the development, use, cross-border movement and marketing of any GMOs and products derived from them;
- taking into account the observations and recommendations of the CSNB in the process of making decisions concerning the import, transit, use, dissemination and marketing of GMOs and products derived from them;

- conducting risk assessments and reviewing submitted risk assessments of GMOs that are the subject of applications submitted to the ANB;
- inspecting and auditing the processes of facilities used in connection with research, development, commercialization, and import/export of GMOs;
- serving as a liaison between national and international organizations in the area of biosecurity, and coordinating the cooperation between national and international institutions, as well as private organizations operating in Burkina Faso;
- creating and providing public access to a database concerning GMOs and their products;
- ensuring public information/awareness and their participation in the decision-making process.

The ONB's function is less precisely defined by law. It is the competent consultative body in the area of biosecurity supervision and education, tasked with alerting the ANB and other competent administrative bodies of "serious risks" posed by a GMO and its products with respect to human and animal health, and the environment. The law does not define what would constitute a "serious risk". The organization and functioning of the ONB is further elaborated by Decree 2015 444 *(8)*. According to the decree, these are the responsibilities of this body:

- implementing a system of monitoring and surveillance for the health, nutritional, agricultural, environmental, ethical and socioeconomic impacts of GMOs;
- alerting the ANB and other competent agencies to the serious risks posed by a GMO to human or animal health, or to the environment;
- promoting public awareness and information/education on biosafety.

The ONB consists of members from several ministries and civil society groups.

The CNSB's function is even less detailed in the law. The law merely designates the committee as the "competent consultative body in the domain of scientific assessment". The organization and functioning of the CNSB is also further defined by decree *(9)*. The CNSB is responsible for evaluating applications for authorization to use GMOs and providing its opinion on the application to the ANB. The CNSB may also evaluate and validate risk management plans proposed by developers and propose measures of its own. It is additionally charged with conducting risk assessment at all phases of the research and development of a GMO and reporting their assessment to the ANB, as well as assessing socioeconomic impacts and compliance with ethical standards.

Additionally in Burkina Faso the use of GMMs falls under Environmental Law and implementing regulations (Loi No006-2013/AN), and requires environmental and social impact assessment.

Active GMM research is currently ongoing in Burkina Faso. Burkina Faso authorized the contained use of a GMM in 2016 (10) and subsequently the limited field release of a GMM in 2019 *(11)*.

European Union and United Kingdom of Great Britain and Northern Ireland

In the European Union (EU), a formal risk assessment is the mechanism by which the risks of the release of a GMO are evaluated. The benefits of such a release are not taken into account within a risk assessment in the EU. The release of a GM insect within any EU Member State is controlled by a directive of the European Parliament and of the Council,

known as the Deliberate Release Directive *(12)*, which regulates the release of all GMOs into the environment. In the case of a non-commercial release, such as a field trial, the decision to approve release would be made at the national level. In the United Kingdom, the decision would be made by the Department for Environment, Food, and Rural Affairs, in consultation with the independent scientific experts of its Advisory Committee on Releases to the Environment, which is responsible for assessing the risks of the technology.

For a commercial release in the EU, there is an initial assessment by one 'lead' Member State, which must be satisfied with the information provided before the consultation is opened up to the other Member States. At the end of the process, the European Food Safety Authority (EFSA) would be asked to provide its opinion on any unresolved scientific issues. Member States must then reach a qualified majority to approve any release based on scientific evidence. Should the Member States fail to reach a decision, the application then passes to the European Commission, which can approve or deny the application based on the scientific opinion of the EFSA. The EFSA has developed *Guidance on the environmental risk assessment of genetically modified animals (13)*, including insects. The Netherlands released a technical evaluation of GMMs in 2017 *(14)*.

India

In India, activities involving GMOs and products derived from them are regulated as per the "Rules for manufacture, use/import/export & storage of hazardous microorganisms/genetically engineered organisms, 1989" (*15)* notified under the Environment (Protection) Act, 1986. The "Rules, 1989" essentially cover the entire spectrum of activities involving GMOs and products derived from them, including their sale, storage, exportation, importation, production, manufacturing, packaging, etc. These rules cover areas of research, as well as large-scale applications of GMOs and their products. These rules are implemented by the Ministry of Environment, Forest and Climate Change (MoEFCC), Department of Biotechnology (DBT) and State Governments though six competent authorities. These include the Recombinant DNA Advisory Committee (RDAC), Institutional Biosafety Committee (IBSC), Review Committee on Genetic Manipulation (RCGM), Genetic Engineering Appraisal Committee (GEAC), State Biotechnology Coordination Committee (SBCC), and District Level Committee (DLC). While the RDAC is advisory in function, the IBSC, RCGM and GEAC are responsible for regulatory approvals, and the SBCC and DLC are for monitoring purposes. IBSCs are constituted by all organizations engaged in recombinant DNA technology. The RCGM functions within the DBT and GEAC; the Apex Committee functions within the MoEFCC .

A series of guidelines to be followed at various stages of GMO development have been adopted under the Rules, 1989 from time to time. Recombinant DNA safety guidelines focusing on research and development activities for GMOs, shipment and importation for laboratory research, etc. were adopted in 1990 and updated in 2017 *(16)*. Guidelines have been issued for research, confined field trials, food safety assessment and environmental risk assessment of GM plants by the DBT and MoEFCC *(16–19)*. Bt Cotton is the only genetically engineered crop approved for commercial cultivation in India.

The new guidelines "Regulations and Guidelines on Biosafety of Recombinant, DNA Research and Biocontainment, 2017" *(16)* provide containment levels for microorganisms, animals, plants, insects and aquatic organisms. Insect biosafety levels (IBSLs) have been prescribed with details of facilities in order to prevent escape and establishment of the experimental arthropods in the natural environment, and ensure the safety of laboratory personnel in the facility. Arthropods to

be considered include, but are not limited to: insects (*Lepidoptera; Coleoptera; Diptera,* e.g., mosquitoes, fruit flies; *Hemiptera*), *Blattodea* and *Arachnida* (ticks and mites). All life-cycle stages (eggs, larvae, nymphs, pupae and adults) should be handled within the appropriate IBSL facility. GM arthropods, or non-GM arthropods that are challenged/infected with GM organisms, are covered in the guidelines.

The policy for regulating genome editing is under discussion in the regulatory committees, as the Rules, 1989 also include new gene technologies in their scope.

India ratified the CPB in 2003 and the Nagoya–Kuala Lumpur Supplementary Protocol on liability and redress in 2014.

Malaysia

The Biosafety Act 2007 (Act 678) *(21)* established the National Biosafety Board to regulate the release, import, export and contained use of LMOs, and the release of their products, with the objective of protecting human, plant and animal health, the environment and biological diversity. The Board consists of the following members: the Secretary General of the Ministry of Natural Resources and Environment, who is the Chairman, and representatives from the Ministries of Agriculture and Agro-based Industry; Ministry of Health; Ministry of Plantation Industries and Commodities; Ministry of Domestic Trade and Consumer Affairs; Ministry of International Trade and Industry; Ministry of Science, Technology, and Innovation; and no more than four other persons who have knowledge and/or experience in any of the disciplines or matters relevant to this Act. A Director General is the Secretary of the Board and carries out the duties required by it.

The stated functions of the Board are to decide on all applications; monitor activities relating to LMOs and the products of such organisms; promote research, development, education and training activities related to biosafety; and establish mechanisms to facilitate the collection, storage and dissemination of data related to LMOs, the products of such organisms and biosafety. The Genetic Modification Advisory Committee has been established to provide scientific, technical and other relevant advice to the Director General.

An application for the approval of any release activity and/or any importation of LMOs is submitted to the Director General, accompanied by a risk assessment, risk management report, and emergency response plan. The risk assessment and risk management reports are in a form prescribed by the Minister. They contain an assessment of the known or likely risks and adverse effects of the LMOs and their products for human, plant and animal health, the environment and biological diversity, and the proposed measures to be undertaken to prevent, reduce or control these risks and adverse effects. The emergency response plan provides safety measures and procedures for the protection of human, plant and animal health, the environment and biological diversity against harm or damage caused directly or indirectly by LMOs or the products of such organisms, as well as all necessary measures to be taken in the event of an emergency.

GMMs were released in Malaysia under regulatory approval in 2010 *(22)*.

Mali

Mali signed the CPB in April 2001 and ratified it in August 2002. A biosafety law, Loi n°08-042 *(23)*, was enacted in 2008, with two implementing regulations adopted in 2010. The competent

authority is the Agency of Environment and Sustainable Development (Agence de l'Environnement et du Devéloppement Durable, AEDD), within the Ministry of Environment, Sanitation, and Sustainable Development.

Implementing Decree N°10-682-P-RM *(24)* determines the methods for the research and development of GMOs both in contained use and in the environment. The national competent authority is also empowered to determine the conditions for the import, transit, containment, environmental release and commercialization of GMOs. The Decree provides detailed procedures and forms for requesting authorization to conduct testing of GMOs. These activities are carried out under the oversight of biosafety inspectors.

Implementing Decree N°10-683-P-RM *(25)* details the responsibilities, composition and procedures of the National Biosafety Committee (Comité National de Biosécurité, CNB), which is the committee within the AEDD that is responsible for GMO matters. The CNB's mission is to ensure compliance with regulations on the import, export, transit, contained use, release or placing on the market of any GMO that will be released into the environment or used for food, feed or processing, a product derived from a GMO, or a GMO that might have dual food or pharmaceutical use. It is responsible for making recommendations and providing opinions to the national competent authority regarding regulatory applications for permission to conduct activities with GMOs. The CNB is composed of a President (Minister responsible for the environment or his representative) and members from the public sector, the private sector, local authorities, professionals, research centres, the farming community, and civil society.

Mexico

Mexico actively participated in the negotiations leading to the Agreement on Biological Diversity and when the CPB was adopted. The Interministerial Commission on Biosecurity and Genetically Modified Organisms (CIBIOGEM) *(100)* was created by Presidential Decree on 5 November 1999 *(27)*. Under Mexican Federal law, CIBIOGEM functions to present suggestions to the National Normalization Commission about Mexican official standards for the research, production, trade, import, export, movement, commercial use and consumption of LMOs; promote, together with the Comisión Nacional para el Uso y Conocimiento de la Biodiversidad (CONABIO; National Commission on the Use and Knowledge of Biodiversity), the establishment of a data bank on the presence and distribution of native species related to LMOs, monitor mechanisms and evaluate the environmental impact, and impact on human and animal health resulting from the production and consumption of LMOs; set up a uniform programme for the inspection of LMO research and production plants; and recommend methods for the dissemination of information regarding the benefits and possible risks to the public associated with the use and consumption of LMOs.

Additionally, the 1999 Decree established the Executive Secretary, the Technical Committee, and the Consultative Council on Biosecurity. The Executive Secretary's responsibilities include, but are not limited to, ensuring that laws regarding biosecurity and the regulations of CIBIOGEM are followed by government institutions; registering LMOs and their products and sub-products; establishing and maintaining an up-to-date registry of LMOs; and establishing and maintaining an up-to-date data bank regarding the presence and distribution of native species related to LMOs. The activities of the Technical Committee are coordinated by the Executive Secretary of CIBIOGEM; these include preparing and suggesting to the Executive Secretary issues and

regulations that have to be submitted for consideration by CIBIOGEM, and, when suggested by CONABIO, reaching agreements with the responsible institutions regarding the performance of risk analyses for LMOs, their products and sub-products.

The regulatory process for the conduct of physically confined outdoor testing of GMMs has been documented *(28)*.

Nigeria

Nigeria signed *the* CPB in May 2000 and ratified it in July 2003. GMOs are regulated by the National Biosafety Management Agency (NBMA), under the National Biosafety Management Act, 2015 *(29)*. The Agency is the country's designated authority on biosafety. It is responsible for providing the necessary regulatory framework for the safe application of modern biotechnology in Nigeria in order to prevent any adverse effects of biotechnology on human and animal health, plants and the environment. The Agency is empowered to grant approvals for import, export, transit, contained use, confined field trials or multi-locational trials. The Agency is also tasked with providing for risk assessments to ensure the safety of GMOs with respect to human health and the environment, as well as to ensure that there are no adverse effects of the technology on socioeconomic and cultural interests. The Act also charges the Agency to develop biosafety guidelines and ensure that the country implements its obligations with respect to biosafety under the CBD, CPB, and other international agreements to which the country is a party.

In 2019, the 2015 Act was amended to expand the scope of oversight of the NBMA to the regulation of gene drives, gene editing, synthetic biology, and bio-security and related matters. To date, Nigeria is the only country in the world to have specific language in its biosafety law that mentions gene drives, gene editing and synthetic biology. Since the application of GMMs to control malaria on the African continent is envisioned to involve the use of gene drives, the Nigerian law is mentioned here, even though no research with GMMs or GDMMs is being conducted in the country.

Uganda

Uganda ratified the CPB in April 2004. To date, there is no biosafety law in the country. Activities involving GMOs are regulated by the Uganda National Council of Science and Technology (UNCST), established in 2008 under the Uganda National Council for Science and Technology Act (UNCST Act) *(30)*. The UNCST's authority only extends to the oversight of research and development up to the field trial stage, under the UNCST Act. While biosafety legislation has been working its way through the parliamentary process for several years, there is currently no legal mechanism for the commercial or large-scale deployment of GMOs. However, an amendment to the National Environmental Management Act in 2019 empowered the National Environmental Management Agency (NEMA), in consultation with the relevant ministry, to develop *Guidelines for risk assessment and environmental introduction of GMOs*. This amendment could be sufficient to guide the development and field trials of GMOs, including GMMs and GDMMs, in Uganda. The law is currently supreme (Section 180) and it has explicit guidance on environmental impact assessment and environmental risk assessment, which are required for approving GMOs and which can be implemented to approve the environmental release of GMOs.

United States of America

The USA is not a signatory agent to the CPB. The country uses its existing national legislation and agencies to regulate LMOs under the Coordinated Framework for Regulation of Biotechnology *(31)*. The Coordinated Framework for Regulation of Biotechnology exists under the Executive Office of the President, Office of Science and Technology Policy, and is guidance and not law in the USA. An update to the Coordinated Framework *(32)* announced the policy of the Federal agencies involved with the review of biotechnology research and products. This notice includes separate descriptions of the regulatory policies of the Food and Drug Administration (FDA), Environmental Protection Agency (EPA), Occupational Safety and Health Administration (OSHA) and United States Department of Agriculture (USDA), as well as the research policies of the National Institutes of Health (NIH), National Science Foundation (NSF), EPA and USDA. It explains how the agencies will seek to operate their programmes in an integrated and coordinated fashion to cover the full range of plants, animals and microorganisms derived using new genetic engineering techniques. To the extent possible, responsibility for product use will lie with a single agency; however, in cases where regulatory oversight or review of a particular product is to be performed by more than one agency, the policy establishes a lead agency and consolidated or coordinated reviews.

The Coordinated Framework was updated in 2017 *(32)*. This update describes the current statutory authorities and regulatory programmes of the USDA, EPA and FDA, and summarizes the role of each agency in regulating biotechnology products. As described, GMOs are regulated by the USDA Animal and Plant Health Inspection Service (APHIS) when there is reason to believe that the GMO may be a plant pest or pose a health risk to livestock *(33)*. APHIS's oversight encompasses bacteria, fungi, viruses, and invertebrate animals such as insects, arachnids and nematodes. The jurisdictions of EPA and FDA differ according to the proposed use of the GMOs (e.g., as pesticides or as biological products for human or veterinary use). The roles of EPA and FDA with respect to mosquito-related products were further clarified by guidance issued in 2017 *(34)*. According to this guidance, FDA regulates mosquito-related products intended to "reduce the virus/pathogen load within a mosquito, including reduction in virus/pathogen replication and spread within the mosquito and/or reduction in virus/pathogen transmissibility from mosquitoes to humans" or "prevent mosquito-borne disease in humans or animals." EPA regulates mosquito-related products intended to "reduce the population of mosquitoes (for example, by killing them at some point in their life cycle, or by interfering with their reproduction or development)". This could designate separate regulatory pathways for GMMs designed for population replacement or population suppression.

The National Environmental Policy Act (NEPA) imposes procedural requirements, including an open public comment phase announced in the USA Federal Register for all Federal agencies to prepare an analysis prior to making a decision on any action that may significantly affect the environment. Depending on the characteristics of a proposal, an environmental assessment (EA) or broader environmental impact statement (EIS) may need to be prepared in connection with the release of GMOs. Threatened and endangered species impact assessment is required under the Endangered Species Act (ESA). Federal regulatory decisions regarding permits for GMO environmental release in the USA are subject to either EA for some trials or EIS for large-scale or programmatic use under NEPA.

Examples are available of EA for GMMs *(35)*, EA for GM insect plant pests *(36)* and EIS for GM insect plant pests *(37)*. EPA issued an Experimental Use Permit in 2020 to allow the release of GMMs at US sites.

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