AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

Guidance for the Use of Genetically Modified Mosquitoes

West Africa Integrated Vector Management Programme

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ECOWAS

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About The AU, AUDA-NEPAD and WAHO

The African Union (AU)

The African Union (AU) is a body of 55 member states that make up the countries of the African Continent. It was officially launched in 2002 as a successor to the Organization of African Unity (OAU), which ran from 1963 to1999. The decision to re-launch Africa's pan-African organisation was the outcome of a consensus by African leaders that in order to realise Africa's potential, there was a need to re-focus attention from the fight for decolonisation and ridding the continent of apartheid hitherto pursued under the OAU, towards increased cooperation and integration of African states to drive Africa's growth and economic development. The AU is guided by its vision of *An integrated, prosperous and peaceful Africa, driven by its own citizens and representing a dynamic force in the global arena [1].*

To realise this vision, the Africa Union developed and adopted a 50-year strategic plan called Agenda 2063 [2]. Agenda 2063 is the continent's strategic framework that aims to deliver on its goal for inclusive and sustainable development and is a concrete manifestation of the pan-African drive for unity, self-determination, freedom, progress and collective prosperity pursued under Pan-Africanism and African Renaissance.

The AU has been steadfast in proposing more enabling and science-based approaches to the challenges of the continent. Its report on gene drives clearly embraces the technology as a realistic option for effective disease control. A constructive development along this path was witnessed at the 29th Ordinary Session of Heads of State and Government of the African Union in Addis Ababa, where pursuant to Decision *Assembly/AU/Dec.649 (XXIX),* the session embraced the gene drive technology as a realistic option for malaria control. The session, in its decision, requested the African Union Commission (AUC), West African Health Organization (WAHO) and African Union Development Agency-New Partnership for Africa's Development (AUDA-NEPAD) to collectively support the initiative [3].

In 2018, through recommendations of the African ministers responsible for science and technology *EX.CL/Dec. 987(XXXII),* the Executive Council of the African Union encouraged member states to harness emerging technologies, including gene drive, in their development initiatives [4].

The decisions above have offered solid policy statements for the continent regarding gene drives for human health purposes, which have impacted discussions in AU member states. It is a basis for a harmonised approach for Africa in the development of policy regulations and guidelines such as this to facilitate the responsible and safe application of the technologies for research and subsequent deployment.

The African Union Development Agency - NEPAD (AUDA-NEPAD)

At the 31st Ordinary Session of the Assembly of African Union Heads of State and Government held in Nouakchott, Mauritania from 25th June to 2nd July 2018, the Heads of State and Government approved the transformation of the New Partnership for Africa's Development (NEPAD) Planning and Coordinating Agency into the African Union Development Agency (AUDA) as the technical body of the African Union with its own legal identity, defined by its own statute [6]. The objectives of AUDA-NEPAD are to: a) coordinate and execute priority regional and continental projects to promote regional integration towards the accelerated realisation of Agenda 2063; b) strengthen capacity of African Union Member States and regional bodies; c) advance knowledge-based advisory support; d) undertake the full range of resource mobilisation; and e) serve as the continent's technical interface with all Africa's development stakeholders and development partners.

The West African Health Organization (WAHO)

The West African Health Organization (WAHO) was established in 1987 when the Heads of State and Government from all fifteen countries in the Economic Community of West African States (ECOWAS) adopted and thereafter ratified the protocol for its creation. WAHO has transcended linguistic borders and hurdles in the sub-region to serve all fifteen ECOWAS Member States. The protocol grants WAHO the status of a specialised agency of ECOWAS and, as guided by its mission statement, 'the attainment of the highest possible standard and protection."

The regional agency is charged with the responsibility of safeguarding the health of the peoples in the sub-region through initiation and harmonisation of relevant policies of Member States, pooling of resources, and in cooperation with one another, maintaining a collective and strategic focus on important health problems of the sub-region.

WAHO has, through its strategic programmes, undertaken measures to combat malaria, malnutrition, HIV/AIDS as well as maternal and infant mortality. It has also spearheaded the prevention of blindness, increased access to medicines and vaccines, epidemiological surveillance as well as training and health information management in the sub-region.

Through its second strategic plan, WAHO is currently implementing various cutting-edge programmes in the sub-region to improve the overall health systems, ensure high-quality health services, develop sustainable financing of health and support institutional development within WAHO itself.

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Foreword

Of all the arthropod-borne diseases, malaria has consistently been the most devastating in Africa. The continent, especially the sub-Saharan region, is the most affected by malaria parasites, which are transmitted by female *Anopheles* mosquitoes. According to a WHO 2020 report, there were an estimated 229 million malaria cases and 409,000 deaths worldwide, more than 90% of these having been in Africa [4]. Starting in 2000, when African Heads of State met in Abuja, Nigeria and agreed on a set of resolutions targeting malaria [5], the global malaria mortality has declined by 60% [4]. In the same period, the annual malaria death toll in Africa declined from 680,000 to 384,000 [4], even though the overall population increased from ~800 million to 1.3 billion people. Most of the gains made against malaria have been attributed to vector control interventions, notably insecticide-treated nets (ITNs) and indoor residual spraying (IRS) [6], though there have also been significant improvements in management of malaria cases and overall socio-economic development.

Economic losses due to malaria in Africa are immense and were once estimated to reach 1.3% of the annual per capita income [7]. Beyond the indirect household costs such as lost work hours and missed school days, more than US$ 3 billion was spent directly on the disease in just 2019 alone [4]. Yet, despite the progress made so far, malaria persists in sub-Saharan Africa, even in places where the coverage of the core interventions is considerably high. The failure of current approaches to eradicate transmission may include inadequate financing, insecticide resistance, sub-optimal levels of user-compliance, high costs for replacements and retreatments of commodities such as ITNs, general weaknesses in the health systems and other factors.

With the advent of the COVID-19 pandemic, there is a significant risk of reversing existing gains [8]. The need for augmented and more sustainable approaches for malaria control has therefore been emphasised so that endemic countries can minimise any disruptions as a result of the pandemic [9].

The emergence of gene drive technologies holds prospects for future deployment to significantly improve control and possibly accelerate efforts towards eradication [10]. Current approaches can be used to either suppress malaria vector populations or to alter them such that they no longer transmit malaria. Due to the biased inheritance of traits, gene-drive modified mosquitoes spread faster than the limits imposed by Mendelian inheritance [11-13]. There are, however, still many unknowns regarding the safety and field-efficacy of these technologies. Thus, further evaluation is necessary for both laboratory and real-field settings. By way of flight, modified mosquitoes could also have negative or positive transboundary impacts depending on the expression of the traits they carry. There will therefore be regional regulatory implications in their deployment.

The West Africa Integrated Vector Management (WA-IVM) Programme was inaugurated on the 15th of August 2018 by AUDA-NEPAD and WAHO. Among its objectives, the programme will address the regulatory challenges of the new technology so that the countries can take full advantage of its merits in the control of malaria transmission by *Anopheles gambiae* complex mosquitoes. A Technical Working Group (TWG) has been constituted under a Steering Committee from among the Chief Executive Officers of the National Biosafety Authorities of countries in the sub-region. To facilitate the development of guidelines for the control of various arthropod vectors, the Technical Working Group has developed this generic regulatory guidance for genetically modified arthropod vectors to provide basic understanding regarding the management of the Control of Arthropod vectors.

The guidance covers policy and regulatory considerations, evaluation of efficacy, biosafety consideration, bioremediation, field site characteristics, ethics considerations, public engagement, regional approaches and capacity strengthening, in order to enhance existing regulatory frameworks and international agreements that are relevant for eventual implementation by Regional Economic Communities (RECs).

In addition to this document, the regulator is expected to use the following guidelines, also prepared by the WA-IVM programme for more specific details:

a. Guidelines for containment facilities for testing of genetically modified mosquitoes;

b. Guidelines for importation, exportation, transfer, handling, labelling and storage of genetically modified mosquitoes;

c. Guidelines for institutional biosafety committees (IBCs);

d. Guidelines for compliance monitoring and inspection of activities involving genetically modified mosquitoes;

e. Risk analysis for the testing and deployment of genetically modified mosquitoes;

f. Ethics guidelines for the use of genetically modified mosquitoes.

Abbreviations and Acronyms

ACT	Artemisinin-based combination therapy
ABNE	African Biosafety Network of Expertise
APET	African Union High Level Panel on Emerging Technologies
AU	African Union
AUDA	African Union Development Agency
CSOs	Civil Society Organisations
CRU	Capacity Research Unit
DNA	Deoxyribonucleic acid
ECOWAS	Economic Community of West African States
EIR	Entomological Inoculation Rate
ERA	Environmental Risk Assessment
FBOs	Faith Based Organisations
FNIH	Foundation for the National Institutes of Health
GDA	Gene Drive Arthropod
GDAs	Gene Drive Arthropods
GDMs	Gene Drive Mosquitoes
GM	Genetically Modified
GMAs	Genetically Modified Arthropods
GMMs	Genetically Modified Mosquitoes
GMOs	Genetically Modified Organisms
GVCR	Global Vector Control Response
IBCs	Institutional Biosafety Committees
ITN	Insecticide Treated Nets
IRS	Indoor Residual Spraying
IVM	Integrated Vector Management
LLIN	Long-Lasting Insecticidal Net
MESTI	Ministry of Environment Science Technology and Innovation
NEPAD	New Partnership for Africa's Development
NGO	Non-Governmental Organisations
RA	Risk assessment
RDT	Rapid diagnostic tests
REC	Regional Economic Community
RECs	Regional Economic Communities
RM	Risk Management
RNA	Ribonucleic Acid
TWG	Technical Working Group
US$	United States Dollar
VBDs	Vector-Borne Diseases
WA-IVM	West Africa Integrated Vector Management
WAHO	West African Health Organisation
WHA	World Health Assembly
WHO	World Health Organization

Glossary

Alleles – two or more alternative forms of a gene that arise by mutation and are found at the same location on a chromosome.

Community engagement (also referred to as public engagement) – the process of working collaboratively with and through groups of people affiliated by geographic proximity, special interest, or similar situations to address issues.

Containment - the action of keeping something under control or within limits. *Contained use could be defined as* any operation undertaken within a facility, installation or other physical structure, which involves living modified organisms that are controlled by specific measures that effectively limit their contact with, and their impact on, the external environment.

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

Gene Drive (three dimensions in its definition): - a process that promotes or favours the biased inheritance of certain genes from generation to generation - any genetic element able to bias its inheritance within a population; a tool to effect certain changes in a population

- ***Phenomenon or Process:*** A gene drive is a phenomenon of biased inheritance in which the prevalence of a genetic element (natural or synthetic) or specific alternate form of a gene (allele) is increased, even in the presence of some fitness cost. This leads to the preferential increase of a specific genotype that may determine a specific phenotype from one generation to the next and potentially spread throughout a population. In other words, a gene drive is a process that promotes or favours the biased inheritance of certain genes from generation to generation.
- ***Material Object:*** A gene drive is composed of one or more genetic elements that can cause the process of biased inheritance in its favour. A gene drive is any genetic element able to bias its inheritance within a population.
- ***Intention:*** A gene drive may be intended as a management tool to effect certain changes in a population. A gene drive may include additional "cargo" elements, in addition to the drive components, that are intended to introduce new trait(s) into an interbreeding population so as to effect a change in the characteristics of the population. A gene drive also may cause effects directly, for example, by inserting into and disrupting a target gene. www.pnas.org/cgi/doi/10.1073/pnas.2020417117

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

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

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 vector-borne disease, as determined by assessing the vector mosquito population. It is described by the frequency of infectious mosquito bites upon a person within some unit of time, such as per day or year.

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

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

Ethical review board – see Ethics committee.

Fitness – description of the ability to both survive and reproduce and is 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 influence the fitness of an organism, then the frequencies of these alleles will change over generations, and the alleles with higher fitness will become more common than the weaker alleles that are less adapted for survival and reproduction.

Gene – a gene is a sequence of DNA or RNA that codes for a molecule and/or has a function

Genetically modified mosquitoes - mosquitoes containing recombinant DNA molecules and includes both vector mosquitoes containing modified microbes and also the mosquitoes, which themselves are genetically modified.

Genetically modified mosquitoes (GMMs) – also called genetically engineered mosquitoes or transgenic mosquitoes – mosquitoes that have heritable traits derived through the use of recombinant DNA technology, which alters the strain, line, or colony in a manner usually intended to result in the reduction of the transmission of mosquito-borne human diseases. GMM is also likely to be characterised 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.

Genotype – the genetic constitution of an organism.

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

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

Integrated vector management (IVM) – a rational decision-making process for the effective and efficient use of a combination of available resources in the management of vector populations so as to reduce or interrupt transmission of vector-borne diseases. See: http://www.who.int/malaria/vector_control/ivm/en/

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

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

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.

Release – freedom from confinement. The environmental release is unfettered access to the environment from previous confinement.

Risk – an uncertain event or condition that, if it occurs, has a potentially adverse effect on a project's objective such as time, cost, scope, quality etc.

Risk analysis – the process of prioritising and classifying risks and then determining which risks require the development of mitigating strategies and/or contingency plans. It reflects the project's tolerance for risk and defines thresholds and tolerance levels in areas such as cost, schedule, staffing, resources, quality etc., which, if triggered, may require the implementation of defined contingency plans. Risk Analysis constitutes three components- Risk Assessment, Risk Management and Risk communication.

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

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

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

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

Transgenic mosquitoes – see genetically modified mosquitoes.

Vector mosquitoes – mosquitoes capable of transmitting a disease-causing pathogen.

Executive Summary

This Guidance document provides direction for the development, testing and deployment of gene drive technology for the control of arthropod-borne diseases. It will be a reference framework for developers, promoters and users of the technology. Its use provides a roadmap for safeguarding human and ethical values, addressing safety concerns, enhancing quality and consistency of procedures and proposing ways for appropriate governance. The guidance is based on the latest research evidence on characteristics of gene drive organisms, best practices for evaluating genetically modified mosquitoes (GMMs) with a particular focus on the gene drive technology, and its potential risks and benefits. In addition to this document, the regulator and all other actors are expected to use all the other relevant guidelines for further details.

Approximately 70% of the world's malaria burden is concentrated in 11 countries;,10 of these are from the African continent while one is from Asia and that is India [4, 14]. According to a WHO 2020 report, there were an estimated 229 million malaria cases and 409,000 deaths worldwide in 2019, more than 90% of these having been in Africa [4]. Starting in 2000, global malaria mortality declined by 60%. Annual malaria deaths in Africa declined from 680,000 to 384,000 [4] even though the overall population increased from ~800 million to 1.3 billion people. Most of the gains made against malaria have been attributed to vector control interventions, notably insecticide-treated nets (ITNs) and indoor residual spraying (IRS) [6], though there have also been significant improvements in management of malaria cases and overall socio-economic development. Despite the progress, substantial malaria transmission persists due to factors such as insecticide resistance, sub-optimal user-compliance, high costs of interventions, general weaknesses in the health systems and several others.

With the advent of COVID-19, there is a significant risk of reversing chalked gains. The need for augmented and more sustainable approaches for malaria control has therefore been emphasised [4]. Besides, malaria-endemic countries must minimise any disruptions of ongoing malaria prevention and treatment efforts as a result of the COVID-19 pandemic.

Gene Drives for Mosquito Vector Control. A gene drive is a phenomenon of biased inheritance, in which the prevalence of a genetic element (natural or synthetic) or specific alternate form of a gene (allele) is increased, even in the presence of some fitness cost [15]. Gene drives can promote or favour biased inheritance and the spread of certain genes and associated phenotypes from generation to generation. Curtis [16] and Serebrovsky [17] first postulated the concept of controlling insect pests and vector populations using a self-sustaining mechanism [18]. Hamilton [19] suggested that a genetically encoded sex-ratio distorter could eradicate a vector population if, for example, an extreme male bias was linked to the Y-chromosome. These and many other later strategies constitute the phenomenon of "Gene Drives", where one or more genetic elements bias their inheritance beyond what is predicted by Mendelian genetics, thus increasing their frequency within a population. Among the many naturally occurring systems with potential to generate gene drives, homing endonucleases have been the most promising [18]. These are highly specific DNA-cleaving enzymes that can laterally transfer genetic sequences to homologous DNA segments lacking the sequences.

Today, the most popular form of homing endonuclease used to produce gene drives is the Clustered, Regularly Interspaced, Short Palindromic Repeats (CRISPR) and CRISPR associated proteins (Cas). This has been demonstrated in mosquito vectors *Anopheles gambiae* and *Anopheles stephensi* [12,13]. The two main gene drive approaches pursued for malaria control are: a) population suppression, which involves restricting the growth of mosquito populations through the spread of recessive lethal and sterility genes or by biasing sex ratios, and b) population replacement, which involves interfering with the ability of the *Anopheles* mosquito to transmit the *Plasmodium* parasite. Both approaches have been demonstrated to be highly efficacious inside laboratories. They also have the potential to offer enormous health benefits, and African countries could become early beneficiaries of the technology. The first product from gene-drive technology that is under development for Africa is for suppressing populations of malaria-transmitting mosquitoes.

A mathematical simulation was done to investigate factors that may affect the spread of gene drives over a one million-square kilometre area of West Africa containing substantial environmental and social heterogeneity [20]. This study predicted that endonuclease genes targeting female fertility could lead to substantial reductions in malaria vector populations on a regional scale, eventually stabilising at ~95% after four years. However, such success requires that factors negatively affecting the fitness gene drive mosquitoes, such as somatic expression of Cas9, its deposition in sperm or eggs leading to damage to the zygote or emergent drive-resistant alleles that restore female fertility are contained [20].

Because mosquitoes are mobile organisms, it will be difficult to conduct contained field trials in each of the malaria-infested countries. Regulation of transgenic insects will have to take into account such transboundary issues and preferably consider a regional approach serving multiple countries in a Regional Economic Community (REC).

The African Union has called for malaria eradication [21] and recommended the continued scientific evaluation of new or improved tools to complement current methods, which mostly rely on insecticides. During such evaluations, the potential risks associated with testing or use of the new tools should be weighed against potential benefits such as improvements in human health and reduced exposure to broad-spectrum insecticides.

This guidance is expected to be used by technology developers, scientists and regulators interested in GMM and other GMAs. The guidance covers key elements relevant to the research and development of GMAs, from the laboratory to field testing, notably, considerations for policy and regulatory requirements, evaluation of efficacy, biosafety, bioremediation, field site characteristics, ethics, public engagement, capacity strengthening and relevant international agreements for implementation by Regional Economic Communities (RECs).

Section I: Introduction

Approximately 80% of the world's population is at risk of one or more vector-borne diseases (VBDs), which together are responsible for 17% of the global burden of disease [22, 23]. Considering the significance of these diseases, the Economic Commission of West African States (ECOWAS) has agreed on the establishment of a West Africa Integrated Vector Management (WA-IVM) Programme. The purpose of this programme is to establish and operationalise a platform for the region to build strong collaborations among member countries on issues relevant to effective control of the vectors. Some of the key elements being considered include biosafety, environment, ethics, regulatory oversight and health systems. The WA-IVM platform also aims to equip and capacitate the region with innovative technologies and new approaches for controlling the arthropod vectors.

Malaria is a life-threatening disease caused by *Plasmodium* parasites and transmitted via bites of infected female *Anopheles* mosquitoes. There are five species of human malaria-causing plasmodium parasites *(Plasmodium falciparum, Plasmodium ovale, Plasmodium malariae, Plasmodium vivax and Plasmodium knowlesi)*, but just *P. falciparum* accounts for ~99% of all malaria cases in sub-Saharan Africa. The main vectors in Africa include *Anopheles gambiae, Anopheles coluzzi, Anopheles funestus and Anopheles arabiensis*, but there are several other *Anopheles* species playing important roles in specific local settings [24]. In 2019, there were an estimated 229 million cases of malaria and 405,000 malaria-related deaths [4]. The WHO Africa region accounted for 94% of the burden. Starting 2000, nearly US$ 40 billion has been invested against malaria, about one-third of this contributed by malaria-endemic countries themselves. In 2019 alone, total spending was US$ 3 billion, which was 45% less than the required US$ 5.6 billion budget [4].

The WA-IVM Programme will use malaria as a pathfinder disease for developing its platform activities. Other vector-borne diseases are less deadly but could result in high rates of morbidity and are considered as potential concerns to be addressed subsequently. For example, dengue fever, which is transmitted by *Aedes aegypti* mosquitoes, is one of the fastest spreading vector-borne diseases in Africa, with significant economic consequences. Others include lymphatic filariasis, yellow fever and Chikungunya virus, which are also transmitted by mosquitoes.

The advent of gene drives has brought new hope and opportunities for accelerating efforts towards malaria eradication. Gene drives can stimulate biased inheritance of specific genes to suppress or alter populations of select organisms, including mosquitoes [11]. Laboratory studies have demonstrated that the technique could be applied to prevent mosquitoes from transmitting the malaria parasite or to significantly suppress and crash such mosquito populations [11]. In addition, mathematical simulations have shown that other than certain concerns such as the potential rise of drive-resistant alleles, the desired genetic constructs could be rapidly driven

through large mosquito populations across landscapes, thereby contributing significantly to sustainable malaria control and eradication, especially if used alongside current interventions [20, 25]. Such an approach would require lower levels of human resources, marginal logistical challenges and lower costs, thus potentially being more cost-effective even in locations currently considered remote.

The purpose of this guidance is to provide direction for the development and testing of this gene drive technology while safeguarding the health of the environment, humans and animals. It is also meant to ensure that stakeholders address relevant ethical and safety issues, enhance the quality and consistency of procedures, and propose ways for appropriate governance. It brings together what is known, based on current research evidence on best practices for evaluating GMAs. The main elements included are policy and regulatory considerations, evaluation of efficacy, biosafety considerations, bioremediation, field site characteristics, ethics considerations, public engagement, regional approaches and capacity strengthening.

It is envisaged that this guidance will be used with reference to other detailed guidelines, and they are intended to enhance existing regulatory frameworks and international agreements relevant to GMAs, as well as the eventual implementation of these agreements by the RECs.

The sustainability of harnessing emerging technologies in Africa will require improved policies, political will, and governance to build appropriate frameworks and strengthen capabilities in various domains, including health, biosafety and ethics. Favourable policies and appropriate regulatory systems at both national and regional levels are essential for supporting research in key areas of interest to African governments.

Section II: Policy and Regulation

Policy Considerations

There have been several high-level meetings and policy decisions calling for increased efforts in the development of innovative tools for controlling arthropod vectors. These include the 2013 meeting of the ECOWAS Heads of State and Government in Yamoussoukro, Côte d'Ivoire, which approved the development of strategies and regulatory initiatives for the management of disease vectors. Other meetings by Heads of State and Government have called for the development of regulations on gene drive technologies as well as new generation insecticides for IRS and long-lasting insecticide-treated nets (LLINs). Additional information on these initiatives is provided in Box 1.

The political pronouncements reflect the commitment of African leaders to finding lasting and sustainable ways of controlling vector-borne diseases. In this regard, the AUDA-NEPAD should promote and support policies for the development of innovative tools to achieve this goal at the national and regional levels. In addition, individual West African countries should develop national policies and strategies for the promotion of effective interventions against arthropod vectors, and ECOWAS should create opportunities for rationalising and harmonising these policies.

One country that has demonstrated strong leadership in the trial of new techniques for malaria vector control is Burkina Faso. It was the first African nation to introduce GM technologies for malaria control in collaboration with international agencies in 2016. After several years of preparations and developments, there has also recently been a release of sterile male *Anopheles* mosquitoes in a small community trial in Burkina Faso to provide learning opportunities for any future releases of actual gene drive mosquitoes. In 2019, Burkinabe scientists, in a collaborative study with the University of Maryland, USA, broke new grounds in mosquito vector control by using genetically engineered fungus to produce spider toxins. The study showed that a naturally-occurring fungus could be engineered to deliver toxins to mosquitoes safely and reduce mosquito populations by more than 99% inside screened enclosures simulating local villages [26]. Overall, the spirit for innovation and research in insect vector control by Burkina Faso is worth emulation by its partner countries in Africa.

Regulatory Considerations

To ensure that countries are able to explore and utilise the potential of existing and new vector control approaches, both AUDA-NEPAD and WAHO will collaborate with partners to strengthen the capacity of regulators and relevant stakeholders in the member states. Such interventions in the framework of ECOWAS will include: a) developing appropriate guidelines for the various phases of product development; b) conducting training in order to deepen the understanding of regulators and relevant stakeholders; c) sensitising beneficiary communities and government officials; d) monitoring and evaluating the impact of interventions; and e) using evidence from West Africa to inform scale-up of IVM programmes in other regions.

The WA-IVM Programme will operationalise the recommendations of the African Union High Level Panel on Emerging Technologies (APET) by building a regional platform and using the gene drive as a pathfinder approach among the technologies on the horizon. Due to the unique nature of the technology, the regulatory pathway being targeted is expected to be a model for other emerging innovations such as the use of Wolbachia-infected mosquitoes for control of *Aedes*-borne diseases like dengue [27,28].

Being a pathfinder technology, new regulatory procedures must be developed to undertake the necessary risk analysis. Given the potential of gene drive mosquitoes to spread to contiguous populations across national boundaries, it is desirable that regional approaches are developed to support testing and regulation of gene drive mosquitoes. This would facilitate multi-country regulatory reviews and authorisation for the technology.

The regulatory capacity of the West Africa sub-region for managing gene drive mosquitoes should be developed through the harmonisation of regulations for regional deployment. This should be done through WAHO under the sponsorship of ECOWAS and the AUDA-NEPAD to ensure the necessary international support. The ongoing initiatives by the WA-IVM Programme, which started in Accra, Ghana, on 15th August 2018, is meant to address this strategic need. A summary of the policy initiatives and regulatory considerations are summarised in Box 1.

This platform will ensure that regulators in agriculture, environment, health and other relevant sectors are best informed to make evidence-based decisions to address the burden of malaria and vector-borne diseases. There is a need for balanced assessments to ensure the safety of the environment, human and animal health without being so restrictive as to lose the potential health benefits of the vector control approaches. This will entail coordination between health and environmental regulators at national and regional levels, as well as close collaborations between these regulators and programme officers from both the environment and health sectors, being the frontline sectors (Box 2). Other relevant agencies will be a) Health Product and Regulatory Agencies, b) Agriculture/Environment Sectors, c) National Disease Surveillance and Prevention, d) other Specific Programme areas, e.g., Neglected Tropical Diseases, e) relevant non-governmental organisations, and f) the Media.

Box 1: Key points relevant to policy and regulation

POLICY

In 2013, during the 42nd Ordinary Session of ECOWAS at Yamoussoukro, Heads of State and Government approved the development of strategies for malaria vector control and regional initiatives on vector management. In July 2017, African leaders committed to invest in the development and regulation of the gene drive technology as well as other new innovations including next generation insecticides for indoor residual spray, rapid diagnostic tests (RDT) and artemisinin combination therapy (ACT).

In 2017, during the World Health Assembly (WHA), WHO called for strengthening vector control globally through increased capacity, improved surveillance, better coordination and integrated action across sectors and diseases. The WHA adopted a resolution for Global Vector Control Response (2017-2030). In 2018, the Executive Council of the African Union called upon Member States to harness emerging technologies including gene drive in their development initiatives

REGULATION

AUDA-NEPAD and WAHO will support Member States in:

- developing appropriate guidelines for the various phases of product development;
- conducting training to deepen the understanding of regulators and relevant stakeholders;
- sensitizing beneficiary communities and government officials;
- monitoring and evaluating the impact of interventions; and
- using evidence from West Africa to scale-up the IVM pprogrammemes to other regions.

Risk analysis for testing and deployment of mosquitoes containing gene drive products

The development of gene drive mosquitoes should involve risk analysis at the different production phases. The concept of "Phased Testing" has been widely advocated for testing and deployment of GM mosquitoes [10,29,30]. The four phases proposed are: small scale laboratory testing, confined field trials, staged open release trials and post-release monitoring. Brief explanations of these phases are presented in Box 3 below. It is, however, important to acknowledge that there are unlikely to be any hard boundaries between the testing phases once the products are outside the laboratory. Even in confined trials, actual confinement may not be perfect, leading to wider releases than intended. Moreover, the staged open release trials should be expected to blend into wider dispersal, requiring expanded surveillance in the post-release phase, possibly beyond the intended release area. The most important decision point is, therefore, at the point of moving the gene drive products out of the laboratory for the first time.

Box 2: Key Stakeholders in the IVM Programmes

- **National Health Products Regulatory Agencies**
  - Medicines Regulatory Authorities
  - Clinical Trials Agencies
  - Vigilance Systems
  - National Health Research Ethics Committees
- **Agencies in the Agriculture & Environment Sector**
  - National Biosafety Agencies
  - National Agricultural Research Systems
  - Environmental Regulatory Bodies
- **National Disease Surveillance and Prevention Programmes**
  - National Malaria Control Programme/Neglected Tropical Diseases Programme
  - Protection of Human Env. Programme
  - National Malaria Research and Training Centers
  - Research and Development Institutions (and Universities)
- **Outreach Institutions**
  - Non-Governmental Organisations (NGOs)
  - Faith Based Organisations (FBOs)
  - Civil Society Organisations (CSOs)
  - Media
  - Local community representatives

For safety and efficacy, the accepted risk analysis procedures (risk assessment, risk management and risk communication) should be applied and completed satisfactorily before the appropriate permits are granted for movement to the next phase.

Evaluation of efficacy of gene drive mosquitoes

For any GDMs to be used as public health interventions, they must be effective in reducing transmission of the targeted pathogen(s) and not be detrimental to the environment, human and animal health. Demonstration of efficacy and biosafety will be a critical determinant in decision-making for deployment. The efficacy of GDMs may be measured by both entomological and epidemiological endpoints (Box 4). An entomological endpoint may include a reduction in the risk of pathogen transmission as measured by specific insect population characteristics, while epidemiological endpoints may include a reduction in the incidence of infection or disease in human populations. Entomological endpoints may be relevant through all phases of testing, while epidemiological endpoints will probably only become significant as research progresses to larger trials under Phase 3 (Staged Open Release). Where possible, mathematical modelling may be used to predict or better understand the potential spread and performance of the GDMs. Such modelling work may also be used for planning the releases in cases.

Box 3: Outline of the Phased Testing Pathway for Gene Drive Mosquitoes

Phase 1: Small-scale laboratory studies for efficacy and safety testing, followed by testing in larger population cages in a laboratory setting conducted under appropriate containment facilities and procedures.

Phase 2: Initiate confined testing in a more natural setting but still under containment conditions that will limit release into the environment.

Phase 3: Staged open release trials. This may involve a series of sequential trials of increasing size, duration and complexity, to be conducted at a single site or multiple sites.

Phase 4: 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.

Note: It is important to acknowledge that there are unlikely to be any hard boundaries between the testing phases once the products are outside the laboratory (Phase 1). Even in confined trials, actual confinement may be imperfect, potentially leading to wider releases than intended. Moreover, the staged open release trials should be expected to blend into wider dispersal of the mosquitoes, thus requiring expanded surveillance in post-release phase, possibly beyond the intended release area

The most direct measure of an entomological endpoint is a reduction in the estimated transmission intensity, i.e., the entomological inoculation rate (EIR). As measuring EIR reductions is impossible during Phase 1 and Phase 2, it will be necessary to infer reductions in EIR by surrogate vector indicators that would contribute to the EIR, such as vector population size, transgene frequency, GDM fitness, or pathogen replication within the vector. Further reference should be made to WHO (2014) and AUDA-NEPAD Guidelines on details of parameters to be considered for assessment for Entomological and Epidemiological endpoints (Box 4).

Cluster-randomised trials are frequently used in evaluating other vector control interventions and are considered the most powerful design for many interventions. However, these designs may be difficult to implement for gene drive mosquitoes, which are expected to increase in frequency and spread geographically, thus limiting the feasibility of assigning villages to either the intervention or control arms. Innovative trial designs that take the dynamic nature of gene drive into account

Box 4: Entomological and Epidemiological Indicators

Examples of Entomological endpoints determined at Phase 3 (WHO, 2015)

- Compatibility with other mosquito control measures
- Direct measures of EIR when possible
- Baseline studies of vector composition and abundance
- For GMMs with drive systems, the rate of spread of a transgene in wild populations and comparison with Phase 1 and Phase 2 model predictions
- Measures of transgene functionality, phenotypic stability and mutation rate

Measures of GDA dispersal

- For population suppression strategies, the rate of suppression of wild populations of mosquitoes

Examples of Epidemiological endpoints determined at Phase 3

- Disease incidence and prevalence measured during intervention trials
- Post-treatment active and/or passive disease incidence and prevalence, (consideration should be made on how long these activities should continue)

Note: Phase 3 here refers to staged open release trials, which may involve a series of sequential trials of increasing size, duration and complexity, to be conducted at a single site or multiple sites

may therefore need to be considered. The decision on these designs and their appropriateness should be agreed upon by the researchers, the institutional biosafety committees and the regulatory agencies. The GDM trials must be designed to allow measurable reductions in an endpoint such as infection incidence. Careful site selection is necessary to increase the likelihood of detecting significant results. Moreover, any potential influence of seasonal and inter-annual variations and spatial heterogeneity of incidence on the trial design must be considered. Lastly, specific "go" and "no-go" criteria for moving forward should be determined, particularly at the stage when the GMAs are first used outside confined laboratory settings. The competent national authorities should ensure independent monitoring and inspection of trials.

It is expected that GDMs will most likely be applied in the context of conventional control measures. Thus, their relative efficiencies should, in part, determine their utility. The effect of other ongoing control measures on the outcomes of the GDM trials must also be considered in the trial design.

Biosafety Considerations

The second major consideration when deciding to use any Gene Drive Arthropod (GDA) as a public health intervention is the safety of the environment, human and animal health. Ensuing biosafety of any GDA requires a two-fold approach: **first** is to ensure the biosafety of the GDA to humans, animals and the environment during phased-testing, and **second** is to develop the appropriate data package to facilitate the biosafety regulatory approval of the GDA from one phase of testing to the next and possibly for final open field release. Different stakeholders may play different roles to address the biosafety considerations. For example, ensuring the biosafety of the GDAs during phased testing is a responsibility that all stakeholders should take part in. On the other hand, the developers will be expected to develop the regulatory data package to support the specific GDA product in question, while actual evaluation and approval would be the responsibility of government regulators.

Risk Analysis comprises three sections: Risk Assessment, Risk Management and Risk Communication (Box 5). This will be an indispensable tool for analysing and making biosafety decisions on the safety of GDAs to humans, animals and the environment throughout the phased testing pathway. It is recommended that Risk Analysis of GDAs takes the following stepwise approaches, as used in environmental risk assessment of GMOs and the ERA publication of European Food Safety Authority [31]:

- **Problem formulation (including identification of hazard and exposure pathways):** begins by considering concerns about risks arising from technical, social and other perspectives. It involves identifying the characteristics of the GM organism that might, based on practical or theoretical evidence, cause harm to the environment and/or human and animal health. Problem formulation ends by determining how the identified harm might manifest and what or who is at risk of this harm, along with an appropriate comparator for the risk.
- **Hazard characterisation:** determining the magnitude of the harm if it were to arise.
- **Exposure characterisation:** determining the likelihood of the hazard occurring.
- **Risk characterisation:** determining the level of risk as to the product of the hazard and the exposure (Risk = Hazard x Exposure).
- **Risk management (RM):** selection of management strategies to alleviate/mitigate any identified unacceptable levels of risks.
- **Risk Conclusion:** This refers to the outcome of the risk evaluation considering any residual risk after feasible risk management and acceptability of that residual risk.
- **Risk Communication:** it is important that the nature of the risk and its effective management or acceptance is communicated effectively to those who have expressed risk concerns leading to the original problem formulation. These steps are further listed in Box 5.

Biosafety compliance during GDA testing

Considerations of biosafety of GDAs may vary depending on the actual phase of testing. For example, in Phase 1 (Laboratory studies, including those using caged arthropod populations), safety considerations will include: a) appropriate site selection, b) acceptable level of exposure of the personnel, c) security features to stop GDAs from escaping the facility and d) appropriate methods for disposing of wastes from the laboratories. Subsequently, risk management measures will include a) using appropriate physical and biological containment facilities for mosquitoes, b) ensuring that the GDA and feed sources are free from human pathogens, and c) ensuring that laboratory staff do not carry mosquito-transmissible-diseases. Further reference should be made to WHO guidelines [29] and relevant AUDA-NEPAD guidelines for specific details on biosafety measures at each phase of the GDA testing pathway.

Box 5: Key Steps in Risk Analysis

- **Risk Assessment**
  - Problem formulation
  - Hazard characterization
  - Exposure characterization
  - Risk characterization (Risk = Hazard x Exposure)
- **Risk management (RM)**
  - Risk conclusion
- **Risk Communication**

Developing Biosafety Regulators Package to facilitate Phase Approvals and open release

Biosafety data for GDAs should be generated at each phase for review and approval before the next phase of GDA testing. For example, at Phase 1 (small-scale laboratory studies), the data should be collected regarding the intended and unintended effects of the GDA. These may include stability of gene inserts, copy numbers, the sequences of flanking ends to detect at new open reading frames, change in larval behaviour, change in oviposition, and fecundity, among others. Further reference should be made to WHO 2014 guidelines [29] and their subsequent updates to cover gene drives, as well as AUDA-NEPAD Guidelines on details of biosafety measures at each phase of the GDA testing pathway.

Risk and benefit analysis: From Phase II (confined field testing) to Phase III (open field releases), risk analysis for GDAs should also consider the broader benefit-risk analysis before decisions are made on large-scale implementation for public health purposes. Specific considerations for action during the testing pathway are summarised in Box 6.

Bioremediation and mitigation measures

Risk analysis provides a determination of the magnitude of risk, after which commensurate risk management measures should be put in place to contain this risk to acceptable levels. An example of risk mitigation could be implementing preventive measures against infections or creating access to effective case management (expanding diagnosis and treatment).

However, in practice, regulators may require additional contingency risk management measures to be identified, tested and put in place to address any extra eventualities or accidents that may arise. These additional contingency measures are referred to as bioremediation or mitigation measures. With respect to gene drive mosquitoes, which can potentially spread into contiguous interbreeding populations,

remediation may potentially become difficult once these mosquitoes are widespread. Remediation options are likely to be case-specific and dependent on the specific gene drive strategy, the phase of GMM testing, the geographical location of testing and the actual risk to be remediated. Applicants should consider remediation options in the context of each stage of testing and ensure that these are appropriately planned and funded.

Box 6: Biosafety Considerations during the GDA Testing Pathway

Phase 1 (Laboratory studies): The risk assessment data should include observations of mosquito behavior and other ecologically-relevant characteristics in small-scale laboratory experiments. The assessment should focus mainly on relevant characteristics of the GDAs themselves. It should include data from specific laboratory experiments assessing pathways to harm.

Phase 2 (Contained field releases): Risk assessment data will be obtained from trials conducted under physically or ecologically confined conditions. The data gathered here will help to reduce uncertainties regarding the GDA characteristics observed in Phase 1, thus allowing assessment of health and ecological effects under more realistic levels of exposure.

Phase 3 (Staged open field trials): Risk assessment data is obtained under more realistic conditions using less confined measures than in the previous phases. In preparation for Phase 4, risk assessment should include other relevant issues such as the potential for the movement of GDAs beyond the boundaries of a release area and the evolution of resistance to the drive. The risk assessment done at this stage will determine the necessary scope of post-implementation monitoring and management.

Comparators: The choice of risk comparators changes in its emphasis as testing moves through the various phases. At each stage a range of comparators may be needed to evaluate risks and performance across different dimensions.

Note: All risk analysis for GDAs should be embedded in a broader benefit-risk framework, and duly completed before any decisions are made to proceed with large-scale implementation for public health purposes.

In certain circumstances, especially after confined or open field releases, the selected remediation strategies may involve scaling up proven vector control methods, such as indoor residual spraying or larval source management, to suppress the vector populations. It is advisable to form partnerships with the national malaria control programmes when designing these mediation programmes. Intense application of standard pesticides might also be a logical remediation strategy for semi-field testing and small-scale releases. Regulators and public health authorities will likely be familiar with these remediation approaches. However, the developers and researchers must plan to have the remediation materials (pesticides, equipment or other requirements) available on-site, along with well-trained staff to implement the remediation. They must also ascertain, in advance, the susceptibility of gene drive mosquitoes to a range of pesticides proposed for the remediation efforts.

Though still under testing, gene drive technology may offer additional remediation possibilities not necessarily available for other biocontrol agents. These may include the use of a "recall" construct [32, 33].

Field site characteristics

The site(s) where efficacy trials will be performed must have, as the predominant malaria vector, the same mosquito species that are targeted by the investigational GMM. This will be particularly important for determining both the entomological and epidemiological impact (Box 8). Data to be collected should enable the assessment of the effects of the investigational genetically engineered product on local vector populations and parasite transmission. However, a final decision on the sites may also include non-technical criteria such as local capacity and community-willingness to work with the project.

Detailed guidelines for site selection for testing genetically modified mosquitoes are captured in a separate guideline document.

Box 7: Bio-remediation

- Risk analysis should include consideration of various remediation options on a case-by-case basis, considering the actual gene drive strategy, the testing phase, the geographical location and the risks identified.
- Researchers are advised to partner with national malaria control programmes to design remediation plans.
- After physically confined and small-scale releases, intense application of standard pesticides might be a logical remediation strategy. Therefore, researchers must make plans to have remediation materials and equipment on site, along with staff trained in their proper administration. It should be ascertained in advance that the gene drive mosquitoes will be susceptible to the chosen pesticide(s).
- In the unlikely case that remediation is also necessary in Phase 3 (after large scale open releases), additional methods may be required such as wide implementation of proven vector control programmes and larval source management.
- It is expected that gene drive technology may offer additional remediation possibilities not necessarily available for other biocontrol agents. These may include the use of a "recall" construct.
- It must be noted that any method based on genetic modification also will be subject to risk assessment and regulatory approval.

Ethical considerations

When dealing with GDA technologies, ethical considerations may include those relevant to research activities, public health practice, the environment and governance. Although the technologies are new and have certain unique features relative to conventional interventions, the impact of the technologies is likely to be experienced by communities rather than just individuals. Any information relating to the ethics of the technology should therefore not be administered to individuals but should instead be provided at a collective level. Another challenge is that although principles of public health ethics could be applied for analysing ethical considerations raised by GDA interventions, the GDA technologies themselves are still at a research stage and cannot, therefore, be considered as interventions for the common good. Universally recognised principles of research ethics, necessary for the protection of human research subjects, should, however, be applied to facilitate reviewing and granting of permits for the research at different stages.

Other considerations associated with GDA technologies include ecological and environmental impacts that transcend individual and community levels. This is particularly important since GDA-based interventions may potentially eradicate or modify individuals of a species, yet there may be insufficient knowledge about the impact on other species or on the ecosystems in general. Lastly, it is important to consider the determination of responsibilities in case of long-term negative impacts resulting from the implementation of GDA interventions. Some of these issues are discussed in Nagoya Kuala-Lumpur Supplementary Protocol on Liability and Redress-Cartagena Protocol on Biosafety [34], but ethical issues should be defined by the relevant parties.

Effectively tackling these different ethical concerns implies the implementation of different mechanisms or measures to handle specific concerns of the different parties and groups, some of whom may be interested mainly in safety issues.

Box 8: The Site Selection criteria

- Geographical and biophysical characteristics: sites that provide opportunities for ecological or geographical separation may be preferable for initial trials. Other relevant factors may include suitability of the terrain and climate
- Distribution of principal vectors in the release area: since gene drive products are species specific, it is important that the targeted vector species is either the dominant or one of the dominant vector species in the selected site
- Location of mosquito larval sites: it is important that aquatic habitats are findable, can be characterised, and monitored to allow the surveillance and risk assessment activities relevant to the GDA
- Climatic conditions: the climate should enable long-term survival and spread of the gene drive mosquitoes without compromising performance of the constructs
- Knowledge of active transmission (and transmission dynamics) of the target disease pathogen at the site: the area should be sufficiently characterized, and the prevailing parasite transmission risk adequately quantified
- Existing surveillance and control systems for both vectors and disease: there should be capability to effectively monitor the existing vector populations, pathogen transmission and impacts of the GDA interventions and intervention packages deployed
- Likelihood of obtaining regulatory, social and political approval for research on GMMs in the study community and surrounding areas: considerations should include the level of regulatory capabilities in the country where the GDAs will be initially released.
- Ability to continue existing vector control practices: GDAs are currently expected to be deployed as part of an integrated vector management programme, alongside current core interventions such as LLINs and IRS. It is therefore important to ensure that these core interventions can continue despite roll-out of GDAs
- Others: other non-technical considerations, such as willingness of community members and other stakeholders to participate in the trials, and availability of local experts capable of managing the various aspects of the interventions, should be taken into account

Box 9: Ethical Considerations

- Researchers should actively engage (through consultations or meetings) with communities, social organizations and others interested in the research
- Researchers should establish an independent group of external ethics experts, including those from involved communities and countries, to advise their projects throughout the research and testing trajectory
- Encourage creation of local community advisory boards and their involvement in decision making processes
- Authorities should establish an ethics advisory group that includes ethics and regulatory experts, civil society, researchers and members of communities to foster inclusive and multi-sectorial discussions on the questions related to GDA
- It is important to demonstrate transparency at all levels to engender public confidence;
- It is important to establish procedures for timely information sharing and feedback
- Establishment of ethics working groups at the regional levels in collaboration with regulatory bodies to reflect on and anticipate controversial or sensitive issues and to provide additional and broader perspectives;
- Establishment or reinforcement of regulatory mechanisms to adequately address safety issues.

Public Engagement

Public Engagement is crucial to ensure public trust and acceptance of new technologies and is, therefore, an essential component of the decision-making process. Important issues to consider for effective public engagement during the development and deployment of new vector control technologies, in particular GDAs, are listed below:

- In applying gene drive technology and supporting regulation that would result in successful technology adoption, it is important that these are conducted under high levels of transparency in order to result in sustainable public acceptance. This is particularly important for emerging technologies in the biotechnology arena that could be used to eradicate or significantly alter populations of a target species.
- There are different levels of engagement, namely: international, continental, regional, national and local. In addition, there are several stakeholder groups who may have direct or indirect interests in the technology; hence different levels of acceptance may be required.
- The nature of effective engagement is context-specific. Therefore, it will be important to enlist local or regional experts who are familiar with the cultures.
- Involving the public at each stage of innovation is critical to ensure that decision-makers, stakeholders and end-users make informed decisions concerning the technologies.
- Applicants must develop a plan of how engagement at various levels will be managed and how the opinions of various stakeholders will be considered when making decisions over the course of a project.
- There are different audiences for engagement. These may include communities living at the trial sites and third parties with legitimate interests in the research. Obligations to these different stakeholders will vary in their ethical significance and may be addressed through a spectrum of activities.
- Community engagement is the appropriate mechanism to acknowledge and respond to the group of stakeholders living in the vicinity of field-testing who are not participating directly as research subjects.
- At each subsequent phase of testing, broader outreach will be required.
- Applicants should seek to learn from local experts and organisations familiar with the communities about the appropriate pathway and extent of engagement.

- National authorities will have requirements for public input and engagement within their processes. Applicants must coordinate their engagement efforts with these regulatory processes.
- During early engagement, applicants should consider asking the community how they wish to be consulted and what they consider to constitute authorisation to proceed with testing. It is important to foster community ownership and identification with the research.

Further regulatory expectations for public engagement are as listed in Box 10. In addition, regulators will ensure that the objectives of projects include the following:

- Reaching a consensus regarding the entomological collections requiring individual consent or community acceptance
- Gathering public knowledge that can inform project activities
- Co-developing project with different stakeholders
- Taking public input into consideration in risk management, and
- Demonstrating accountability by ensuring that stakeholder complaints can be addressed in a transparent and systematic manner.

Box 10: Regulator expectations for public engagement

Regulators will ensure applicants have evidence of:

- Awareness creation and consultation strategies, including the need for engagement and feedback
- Mechanisms for getting feedback from the general public and other stakeholders
- Stakeholder engagement experts and communication experts supporting the project
- Dedicated budget for engagement
- Community acceptance to carry out any relevant activity in the community

Section III: Regional Approaches

Due to the flight habits of mosquitoes and given that the intention of the gene drive technology is for GDAs to spread beneficial modifications throughout contiguous interbreeding populations and species, it is expected that the modification will eventually spread across national borders. It is therefore imperative that regional approaches to testing of gene drive mosquitoes be put in place to facilitate a multi-country regulatory review and authorisation process. This regional strategy should receive the necessary support from government authorities and all other relevant stakeholders.

One key point of consensus in all the high-level decisions is that vector control should be handled from an inter-sectoral perspective rather than being a single sector responsibility. In this case, the ministries of health are to collaborate with Ministries of Environment, National Biosafety Authorities and other relevant ministries and agencies in their implementation of vector control programmes. This is one of the pillars of the Global Vector Control Response Strategy [35].

In the case of West Africa, a governance structure at the regional level is established around the WA-IVM Programme. The purpose of the WA-IVM Programme is to implement AU, ECOWAS Heads of State and Government decisions and the World Health Assembly resolutions on the management of disease vectors. The integrated approach will address most of the challenges that have been identified with previous vector control interventions and, in addition, establish a regional governance mechanism at the level of ECOWAS through its technical agency on health, the WAHO.

Operationalisation of this structure will require the development of appropriate regional guidelines and other documents to facilitate the work of the governance structure. There are regional networks in different domains (drugs, biosafety, and ethics, among others) that will have an important role in developing these guidelines as well as procedures for regional reviews. Where implementation concerns more than one country, a joint review will be appropriate. The regional platform should establish an efficient and timely system for information sharing.

At the national level, regional decisions may be adopted to inform national authorisations. Further summary for a regional programme for IVM is presented (Box 11).

Box 11: Summary of Regional Approaches for Integrated Vector Management (IVM)

- There should be a high-level consensus for regional approach for IVM
- A multi-sectoral approach is necessary to pursue the IVM agenda
- A regional platform for IVM is required to champion important IVM agenda across countries
- Regional guidelines and technical documents should be developed to support IVM initiatives
- Existing regional regulatory network should lead the production of guidelines and organization of a regional review process
- Joint review and monitoring are needed where more than one country is concerned with the implementation of a specific programme
- The regional platform should establish an efficient information system for use by all member countries

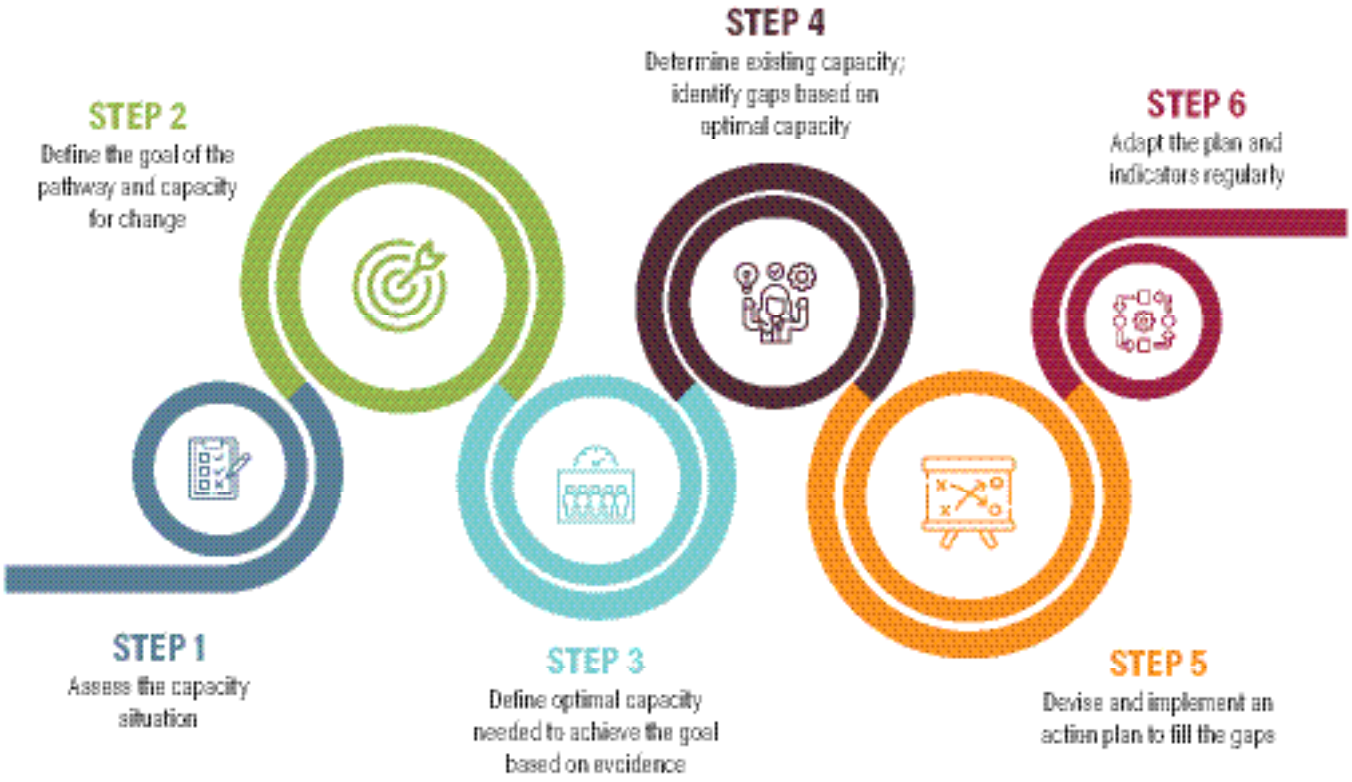
Section IV: Capacity Strengthening

Sustainable development in Africa depends on its capacity to innovate and develop solutions to address priority challenges on the continent. Conducting trials and implementing successful GDA interventions will require strong intellectual understanding, cultural intimacy and logistical capabilities in locations where the programmes are being implemented. Given the breadth of activities that have been described above, member countries require personnel and facilities to perform key scientific, regulatory, ethical and training activities. Further sub-specialisations will be required, such as medical entomology, molecular biology, statistics and diagnostics, among others. All these cannot be fully achieved without well-trained personnel at national and regional levels.

The 6-step approach (Fig. 1) defines the goals of capacity building and/or strengthening whilst assessing existing capacities. This gives measurable indicators in the capacity building plan that will determine if, indeed, the goal has been achieved. For instance, during trial design, 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 take advantage of existing national capacities. When specific abilities are lacking, a strategy for training national personnel to satisfy these needs should be planned and undertaken. While the responsibility of training people primarily lies with the individual countries and the regional block, all other key stakeholders should contribute to ensuring the success of the initiatives.

Sufficient lead-time for training must be part of the trial design, and a commitment to retain trained personnel in the trial will be important to ensure continuity and allow for a deep understanding of and involvement in the project. These personnel will play vital roles not only in trial conduct but also in regulatory interactions and long-term monitoring activities.

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



Proposed steps in building capacity as an essential component of control measure durability in testing Genetically Modified Arthropod vectors – modified from "The Capacity Research Unit (CRU)'s 5-step approach" of the Liverpool School of Tropical Medicine https://www.lstmed.ac.uk/news-events/media/the-capacity-research-unit-cru-our-five-step-approach)

Figure 1: The 6-step approach to capacity building and strengthening

A wide range of factors contributes to limited regulatory capacity. Examples may include a) lack of or outdated legislation, regulations and guidelines that meet internationally acceptable standards, b) limitations in terms of human and financial capacity, and c) lack of the necessary infrastructure to execute the training mandate. Thus, during the period where legal instruments are reviewed, finalised and passed, it is valuable to initiate biosafety capacity building for all aspects of biosafety oversight, notably in the current case, the development and deployment of GDAs.

Once legal changes are approved by stakeholders and the amended provisions are approved through the legislative procedures, biosafety training should start. This will ensure that capacity exists in the national biosafety structures to process applications for contained laboratory studies of mosquitoes, confined field trials, open stage release and post-release monitoring of mosquitoes.

Implementing procedures for contained and confined research and development build experience with risk assessment, risk management and risk communication that is valuable to developing workable legislation for general use of GM organisms. National biosafety offices are encouraged to document trained personnel and ensure that they are given an opportunity to use their biosafety skills after training activities.

Institutional capacity should be interpreted to also include physical facilities and systems. Even though construction of major facilities will be beyond the resources of most trials, incremental improvements can be made on the facilities, for example, by the provision of scientific equipment, computers and software required for the trials or making improvements in biosafety to achieve risk mitigation goals. Some structures, such as arthropod containment laboratories for entomological studies, may be so expensive as to require a more structured fund-raising for dedicated infrastructure development budgets. Where possible, multiple sources of funding may be used to create shared facilities for use by multiple projects. Coordinating investments for such infrastructure will provide a strong foundation for further research and development activities.

References

1. African Union. *An Integrated, Prosperous and Peaceful Africa, driven by its own citizens and representing a dynamic force in the global arena.* 2021 [cited 2021 January 2021]; Available from: https://au.int/en/overview.
2. African Union, *Agenda 2063 The Africa we want in 2063 - Report of the commission on the African Union.* 2015.
3. AUDA-NEPAD. *Who We Are; Our Mandate.* 2021 [cited 2021; Available from: https://nepad.org/who-we-are.
4. World Health Organization, *World Malaria Report 2020.* WHO, 2020. World Health Organization.
5. World Health Organization, *The Abuja Declaration and the plan of action. An extract from the African Summit on Roll Back Malaria, Abuja WHO/CDS/RBM/2000.* 2000.
6. Bhatt, S., et al., *The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015.* Nature, 2015. 526(7572): p. 207-211.
7. Gallup, J.L., *The economic burden of malaria.* Am J Top Med Hyg, 2001. 64(90010): p. 85-96.
8. Sherrard-Smith, E., et al., *The potential public health consequences of COVID-19 on malaria in Africa.* Nature medicine, 2020. 26(9): p. 1411-1416.
9. World Health Organization, *Tailoring malaria interventions in the COVID-19 response.* WHO, 2020.
10. National Academies of Sciences, E. and Medicine, *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values,* 2016: National Academies Press.
11. Nolan, T., *Control of malaria-transmitting mosquitoes using gene drives. Philosophical Transactions of the Royal Society B*, 2021. 376(1818): p. 20190803.
12. Gantz, V.M., et al., *Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Anopheles stephensi.* Proceedings of the National Academy of Sciences, 2015. 112(49): p. E6736-E6743.

13. Hammond, A., et al., *A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector Anopheles gambiae.* Nature biotechnology, 2016. 34(1): p. 78.

14. World Health Organization, *World Malaria report 2018.* WHO, 2018. Geneva.

15. Alphey, L.S., et al., *Opinion: Standardising the definition of gene drive.* Proceedings of the National Academy of Sciences, 2020. 117(49): p. 30864-30867.

16. Curtis, C., *Possible use of translocations to fix desirable genes in insect pest populations.* Nature, 1968. 218(5139): p. 368-369.

17. Serebrovsky, A., *On the possibility of a new method for the control of insect pests.* Sterile-male technique for eradication or control of harmful insects. Proceedings of a panel on application of the sterile-male technique for the eradication or control of harmful species of insects, organised by the Joint FAO/IAEA Division of Atomic Energy in Food and Agriculture and held in Vienna, 27-31 May 1968., 1969: p. 123-237.

18. Hammond, A.M. and R. Galizi, *Gene drives to fight malaria: current state and future directions.* Pathogens and global health, 2017. 111(8): p. 412-423.

19. Hamilton, W.D., *Extraordinary sex ratios.* Science, 1967. 156(3774): p. 477-488.

20. North, A.R., A. Burt, and H.C.J. Godfray, *Modelling the suppression of a malaria vector using a CRISPR-Cas9 gene drive to reduce female fertility.* BMC biology, 2020. 18(1): p. 1-14.

21. African Union, *Africa Health Strategy 2016–2030*, 2016: Addis Ababa.

22. Organization, W.H. and UNICEF, *Global vector control response 2017-2030.* 2017.

23. Golding, N., et al., *Integrating vector control across diseases.* BMC medicine, 2015. 13(1): p. 249.

24. Sinka, M.E., et al., *The dominant Anopheles vectors of human malaria in Africa, Europe and the Middle East: occurrence data, distribution maps and bionomic précis.* Parasites & Vectors, 2010. 3(1): p. 117.

25. Eckhoff, P.A., et al., *Impact of mosquito gene drive on malaria eradication in a computational model with explicit spatial and temporal dynamics.* Proceedings of the National Academy of Sciences, 2016: p. 201611064.

26. Lovett, B., et al., *Transgenic Metarhizium rapidly kills mosquitoes in a malaria-endemic region of Burkina Faso.* Science, 2019. 364(6443): p. 894-897.

27. Ryan, P.A., et al., *Establishment of wMel Wolbachia in Aedes aegypti mosquitoes and reduction of local dengue transmission in Cairns and surrounding locations in northern Queensland, Australia.* Gates open research, 2019. 3.

28. Indriani, C., et al., *Reduced dengue incidence following deployments of Wolbachia-infected Aedes aegypti in Yogyakarta, Indonesia: A quasi-experimental trial using controlled interrupted time series analysis.* Gates open research, 2020. 4.

29. World Health Organization, *Guidance framework for testing of genetically modified mosquitoes.* WHO Programme for Research and Training in Tropical Diseases, 2014.

30. James, S., et al., *Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for eradication of malaria in sub-Saharan Africa: recommendations of a scientific working group.* The American journal of tropical medicine and hygiene, 2018. 98(6_Suppl): p. 1-49.

31. EFSA Panel on Genetically Modified Organisms, *Guidance on the environmental risk assessment of genetically modified animals.* EFSA Journal, 2013. 11(5): p. 3200.

32. Burt, A., *Site-specific selfish genes as tools for the control and genetic engineering of natural populations.* Proceedings of the Royal Society of London. Series B: Biological Sciences, 2003. 270(1518): p. 921-928.

33. Wu, B., L. Luo, and X.J. Gao, *Cas9-triggered chain ablation of cas9 as a gene drive brake.* Nature biotechnology, 2016. 34(2): p. 137-138.

34. Nijar, G.S., *The Nagoya–Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety: An analysis and implementation challenges.* International Environmental Agreements: Politics, Law and Economics, 2013. 13(3): p. 271-290.

35. World Health Organization, *Global vector control response 2017-2030.* World Health Organization, 2017.

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