What is risk assessment?

Target Malaria is an innovative project to reduce the population of malaria-transmitting *Anopheles* mosquitoes in sub-Saharan Africa, and thereby reduce the transmission of the disease. Currently, we are evaluating a series of approaches involving the use of genetically-modified strains of the *Anopheles* mosquito. This work is still at an early stage, but our computer models indicate the potential to significantly reduce the numbers of these mosquitoes, and therefore the transmission of malaria, within a timeframe of years following a release of self-sustaining genetically modified mosquitoes. We are taking a phased approach to our developmental pathway, where each stage builds on lessons learnt from previous ones for the incremental evaluation of the safety and efficacy of our technology.

Our project's ability to move through each evaluation phase is subject to national regulations, ethical approvals, and acceptance of communities directly impacted by the activities. We are committed to abide by international guidelines and to work in collaboration with regulatory authorities in all the countries where we work.

Defining risk assessment

Risk is the chance that a person or the environment will experience an adverse impact or harm on exposure to an event. It is measured as a combination of the probability of harm occurring and the severity of that harm.

> **Minimising any potential risks from our technology is of paramount importance to us. We are working to ensure that any concerns that may present a plausible pathway to potential harm can be addressed in our development pathway. A plausible pathway to potential harm has a series of identifiable and logical steps that could lead to an adverse outcome.**

Risk analysis is fundamental to Target Malaria's decision making, and includes the key elements of risk assessment, risk management, and risk communication throughout our phased development pathway.

- **Risk assessment** identifies potential pathways to harm that could have adverse health or environmental effects, evaluates the likelihood and magnitude of such potential harms occurring and highlights any further areas of uncertainty.

- **Risk management** activities identify and implement suitable measures that can avoid or mitigate identified risks.

- **Risk communication** helps to inform communities and relevant stakeholders if risks have been identified that would impact them and details any risk mitigation in place.

Modelling, literature reviews and extensive laboratory testing help us to better understand risks or areas of uncertainty before we apply to relevant regulatory authorities for a permit to import a mosquito strain into one of our African partner institution laboratories, or to seek permission to carry out a small-scale release study.

The purpose of such small-scale release studies are to evaluate performance at various stages of development stages of development and thus answer fundamental questions on fundamental questions on mosquitoes' fitness, mating effectiveness and survival. As with our laboratory studies, Target Malaria's field releases are approached in a step-wise manner, starting with self-limiting strains before any work with self-sustaining strains is undertaken.

International risk assessment framework for living genetically modified organisms

The **Cartagena Protocol on Biosafety to the Convention on Biological Diversity** is an international agreement that aims to ensure the safe handling, transport and use of modified organisms developed by using novel technologies. The Cartagena Protocol provides a framework for risk assessment to evaluate the potential for adverse effects to the protection goal of biological diversity, whilst also taking potential risks to human health into account.

The countries where Target Malaria currently operates have ratified the Cartagena Protocol, and the guiding principles for risk assessment aim to ensure that countries are provided with the information necessary to make informed decisions on the import and use of such organisms in their territory. Many countries have adopted the Cartagena Protocol, and have translated it into national laws to regulate genetically modified organisms or have drafted regulatory frameworks in advanced stages of development.

In many legislative jurisdictions, such as the European Union, the use of modified organisms in contained research facilities is regulated under a distinct legal framework. Guidance documents for risk assessment have been developed by national regulatory bodies, as well as by international organisations and standard setting bodies, while experts in the field publish in scientific journals to ensure established principles are frequently revisited to keep pace with technological change.

Risk analysis of our work

Our project employs a phased development pathway, with risk-based evaluation of scientific evidence and data for each phase. As part of our risk analysis process, the project listens to concerns of the communities in which we work. For potential hazards perceived by those communities, we investigate plausible pathways to harm as a way to address and respond to their concerns.

The project draws on external scientific advice and independent risk assessment to inform its phased development pathway. For example, two independent ecological risk assessments commissioned by the Foundation for the National Institutes of Health (FNIH) were carried out for the contained use and for the small-scale release of a genetically modified sterile male *Anopheles* mosquito strain by the Commonwealth Scientific and Industrial Research Organisation (CSIRO), which is not affiliated with Target Malaria.

In both cases, the CSIRO risk assessment[1] indicated that those risks were at levels that would be negligible or manageable through the implementation of practical measures practical measures taken by the project:

- Negligible: "Risk is of no discernible concern and there is no present need to invoke actions for mitigation" (page 50)

- Manageable: A management plan addresses the question: "Can the risks posed by a proposed dealing be managed in such a way as to protect the health and safety of people and the environment" (page 54)

Field studies will only be undertaken when evidence-based risk assessments for human and environmental health have been conducted by the relevant national authority for biosafety in project countries, in accordance with the appropriate laws. The project will provide the evidence required to support the process, in addition to risk assessments carried out by the project or a third party.

Environmental risk assessment

Environmental protection goals arise from international agreements and national legislation and policy on biological diversity and the environment. We translate these goals into measurement endpoints for risk assessment.

These include, for example, the potential for an ecological displacement to occur following the population suppression of malaria mosquitoes using modified insects, the potential for insecticide resistance to develop in the released

mosquitoes or the potential effects on other species in the food chain. These concerns can be addressed by a technical evaluation of the pathways to harm consisting of the steps needed for an adverse effect to occur. These analyses help to establish the evidence required to inform risk assessment through laboratory and field studies, quantitative modelling, literature review and elicitation of expert opinion.

Health risk assessment

We are developing our technology using a step-by-step approach. Each step involves looking at potential impacts on human and animal health as part of the broader environmental risk assessment. For example, we have designed our laboratory studies based on assessment of identified potential hazards, which helped to support the CSIRO independent assessment[2] of risk to human health[3] for the first phase of our development pathway: the sterile male (which carries a modification that prevents egg development after mating and fertilisation).

CSIRO concluded that the risk assessment results do not indicate the need for additional risk management measures beyond surveillance activities, which are already planned by the project. These studies also concluded that the sterile male strain had neither increased potential for disease transmission nor increased insecticide resistance when compared to unmodified mosquitoes.

Socioeconomic and public health impact assessment

To complement the environmental and health risk assessment process, the socioeconomic and public health impact of the project is also assessed. We try to identify the key social, economic and public health issues that affect the project or that can be affected by the project. These include evaluation of potential impacts – whether positive or negative – of our project on, for example, livelihoods, land use, tourism, trade, employment, public health, governance systems, cultural heritage and social cohesion.

Beyond risk assessment: the risk of current interventions and the risk of doing nothing

As well as acknowledging potential risks from the release of genetically modified mosquitoes, it is also important to consider the risk of relying exclusively on existing malaria interventions, which, although crucial to the control of malaria, have been recognised as insufficient by themselves to lead to further declines in the incidence of the disease[4].

Resistance of mosquitoes to insecticides and of the malaria parasite to drugs is also an important risk that needs to be taken into account. There is a pressing need to develop and assess new complementary technologies that together with existing tools have the potential to significantly reduce the numbers of malaria mosquitoes, and thereby the transmission of malaria.

If we do not act, it is likely that there will berisk to the human population from ongoing transmission, and potentially even resurgence of malaria transmission.

1 Government of Australia, Office of the Gene Technology Regulator *http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/risk-analysis-framework*

2 *https://publications.csiro.au/rpr/pub?pid=csiro:EP153254*

3 Page 2 of CSIRO risk assessment *https://targetmalaria.org/wp-content/uploads/target-malaria-independent-ecological-risk-assessement-small-scale-release-sterile-male-executive-summary.pdf*

4 World Health Organization (WHO) Position Statement Evaluation of genetically modified mosquitoes for the control of vector-borne diseases - 2020 *https://www.who.int/publications/i/item/9789240013155*

World Health Organization (WHO) Benefits, future scenarios and feasibility. Executive summary, WHO Strategic Advisory Group on Malaria Eradication - 2019 *https://www.who.int/publications/i/item/WHO-CDS-GMP-2019.10*

Feachem, R., Chen, I, Akbari, O. et al. Malaria eradication within a generation: ambitious, achievable, and necessary. The Lancet Commissions Volume 394, ISSUE 10203, P1056-1112 (2019) DOI link: *https://doi.org/10.1016/S0140-6736(19)31139-0 https://www.thelancet.com/commissions/malaria-eradication*

World Health Organization (WHO) Vector Control Advisory Group, Fifth Meeting - 2017