Considerations for first field trials of low-threshold gene drive for malaria vector control

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RBM VCWG
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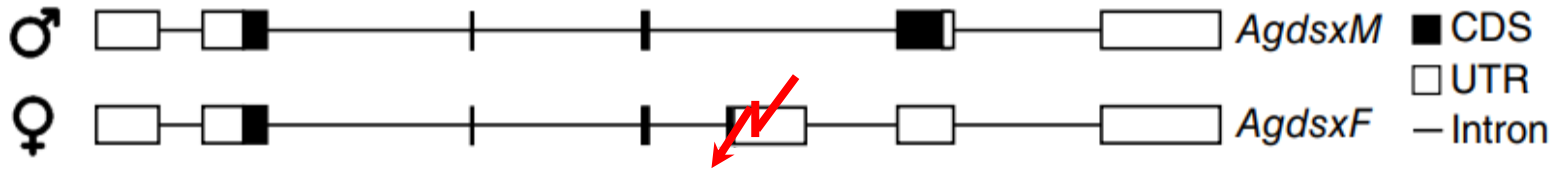
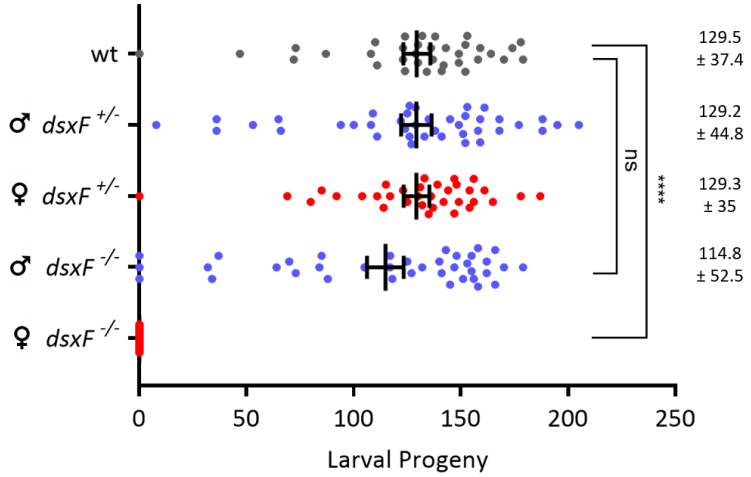
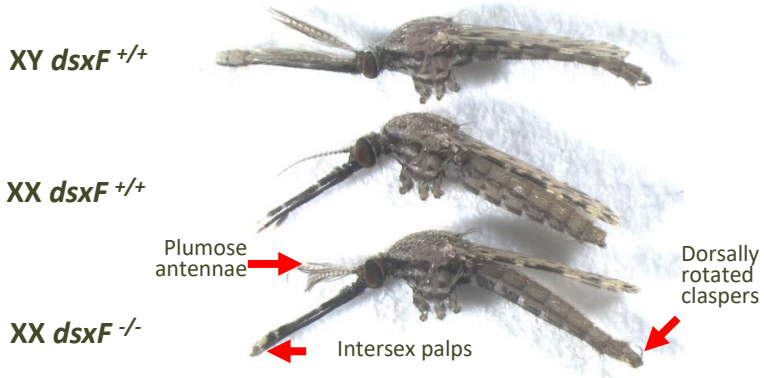
Advancing Best Practices in Genetic Biocontrol Technology

USA

An. gambiae females homozygous for *doublesex* mutations are sterile and non-biting

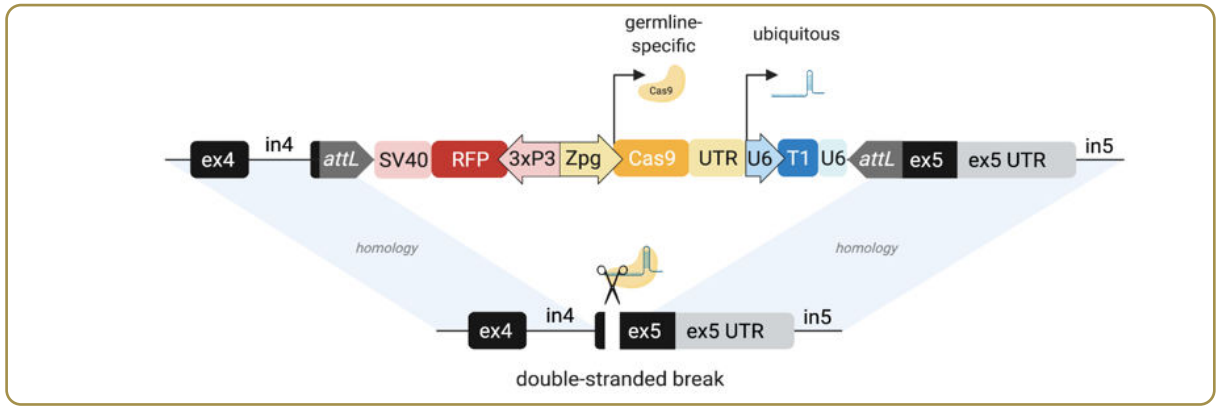


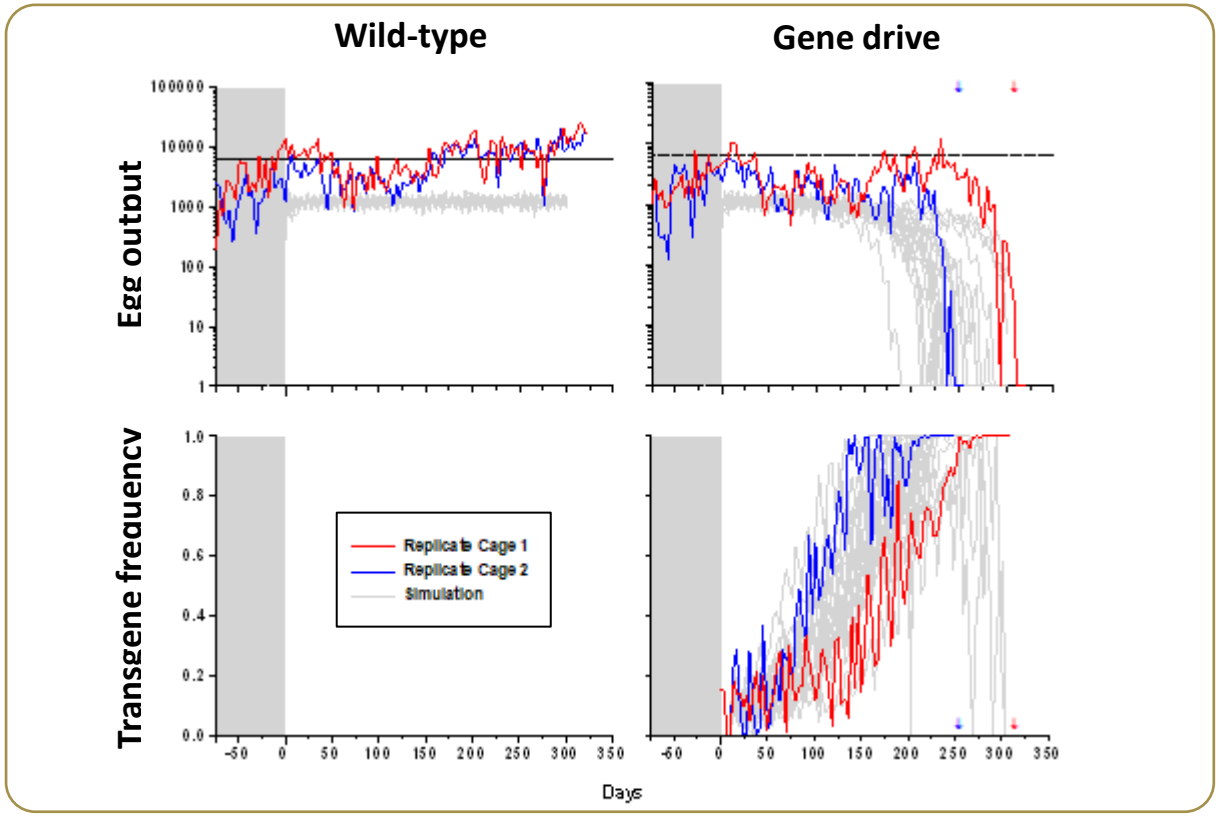




Kyrou *et al.* (2018) DOI: 10.1038/nbt.4245

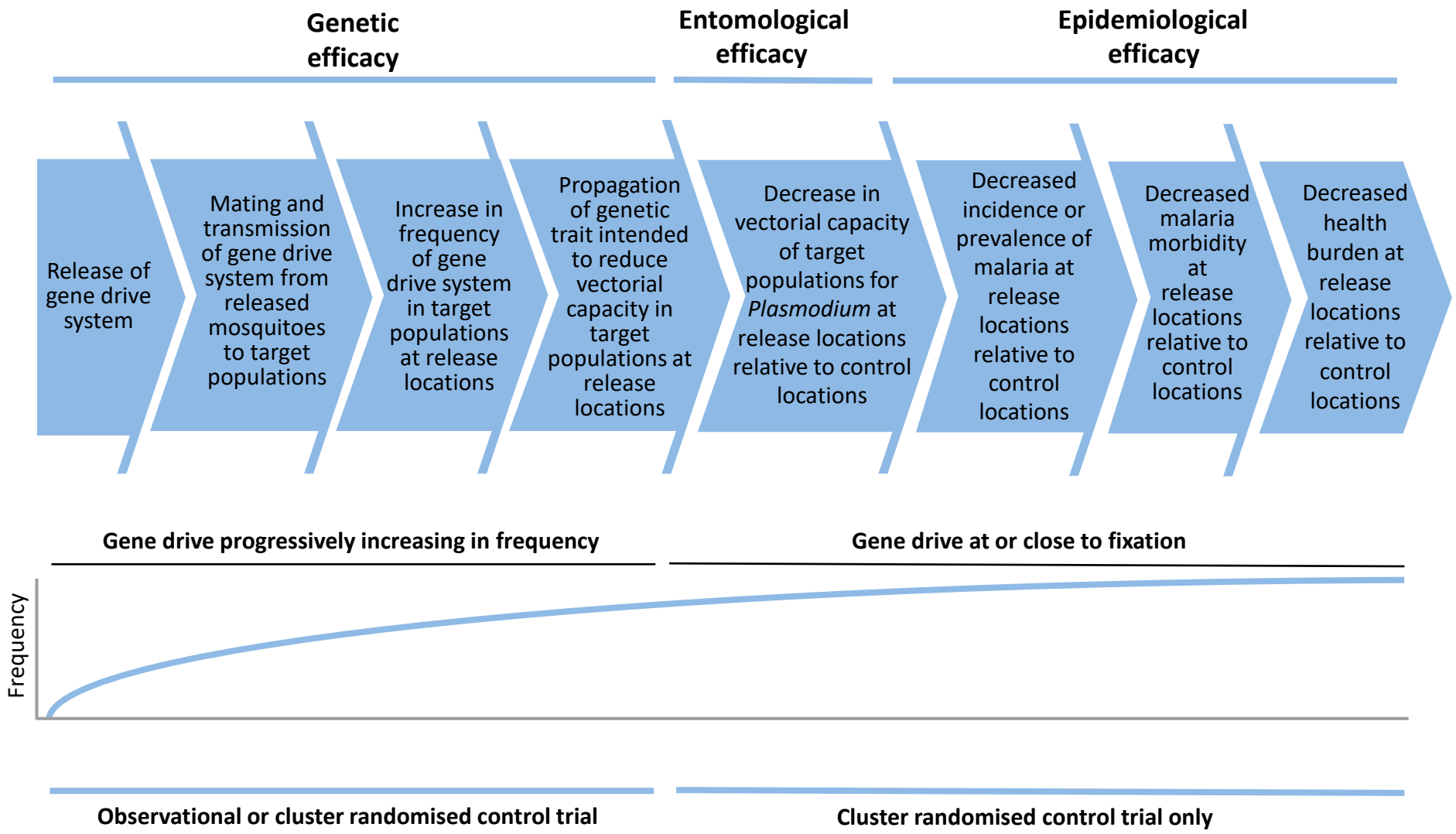
Low-threshold, self-sustaining, population suppression gene drive at *doublesex* locus crashes *An. gambiae* populations in large cages



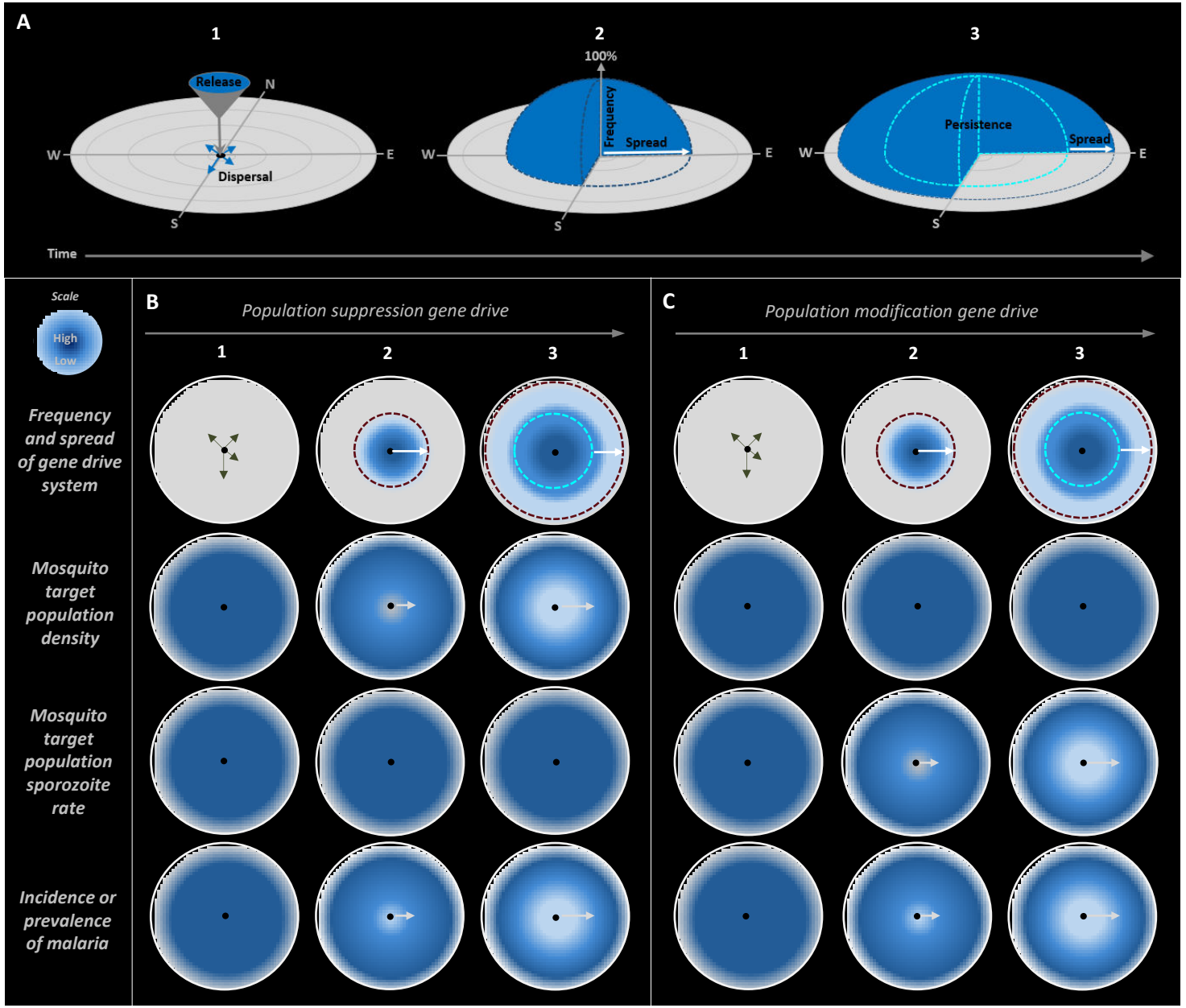


Weekly release of 800 individuals; overlapping generations; semi-field conditions; Hammond, A. *et al.* (2021) 10.1038/s41467-021-24790-6

Causal chain of events for action of gene drive in malaria vector control



Expected behavior and impact of low-threshold gene drive systems upon field release



Disparate types of gene drive

Initial gene drive field trials considered in context of both population suppression and population modification

	Self-limiting	**Self-sustaining**
High-threshold	Spatially restricted-(localized) Temporally restricted (transient)	Spatially restricted (localized) Temporally unrestricted (persistent)
Low-threshold	Spatially unrestricted (non-localized) Temporally restricted (transient)	***Spatially unrestricted (non-localized)*** ***Temporally unrestricted (persistent):***

How to avoid spillover effects in first field trials and subsequent ones?

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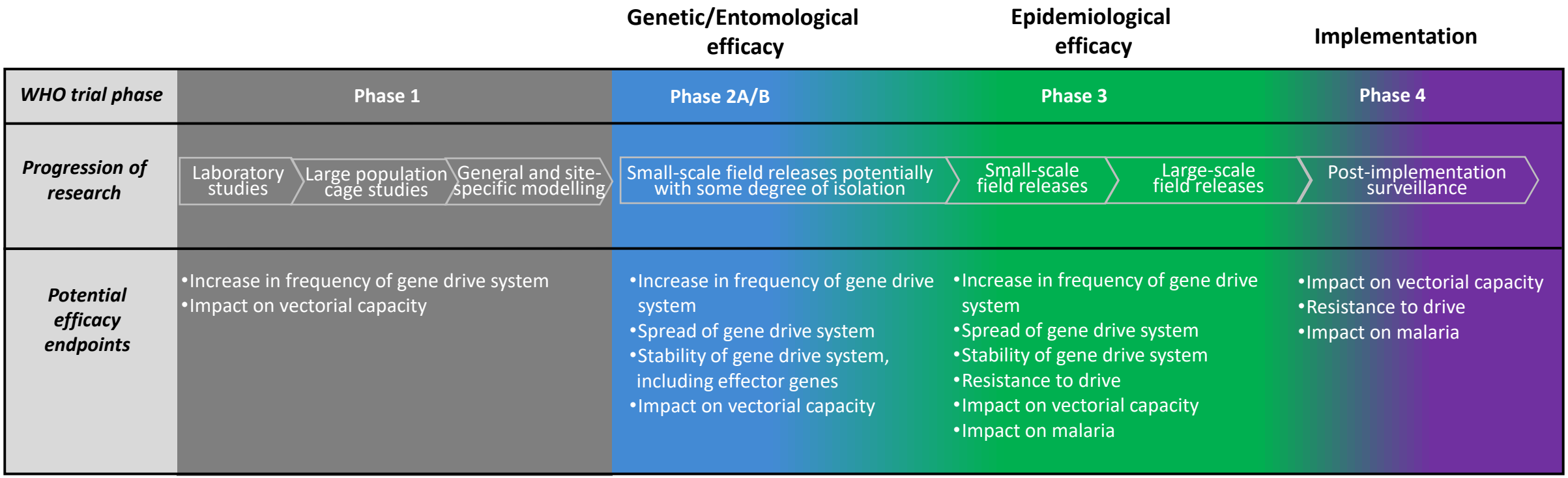
WHO phased testing pathway for low-threshold gene drive system from laboratory studies to implementation



…in the case of self-sustaining, non-localizing [gene drive modified mosquitoes] GDMMs, field testing may better be conceived of as a continuum of expanding releases…a biologically relevant precedent can be found in the testing of exotic biocontrol agents that are also expected to spread and persist in the environment after release. **WHO (2021)**

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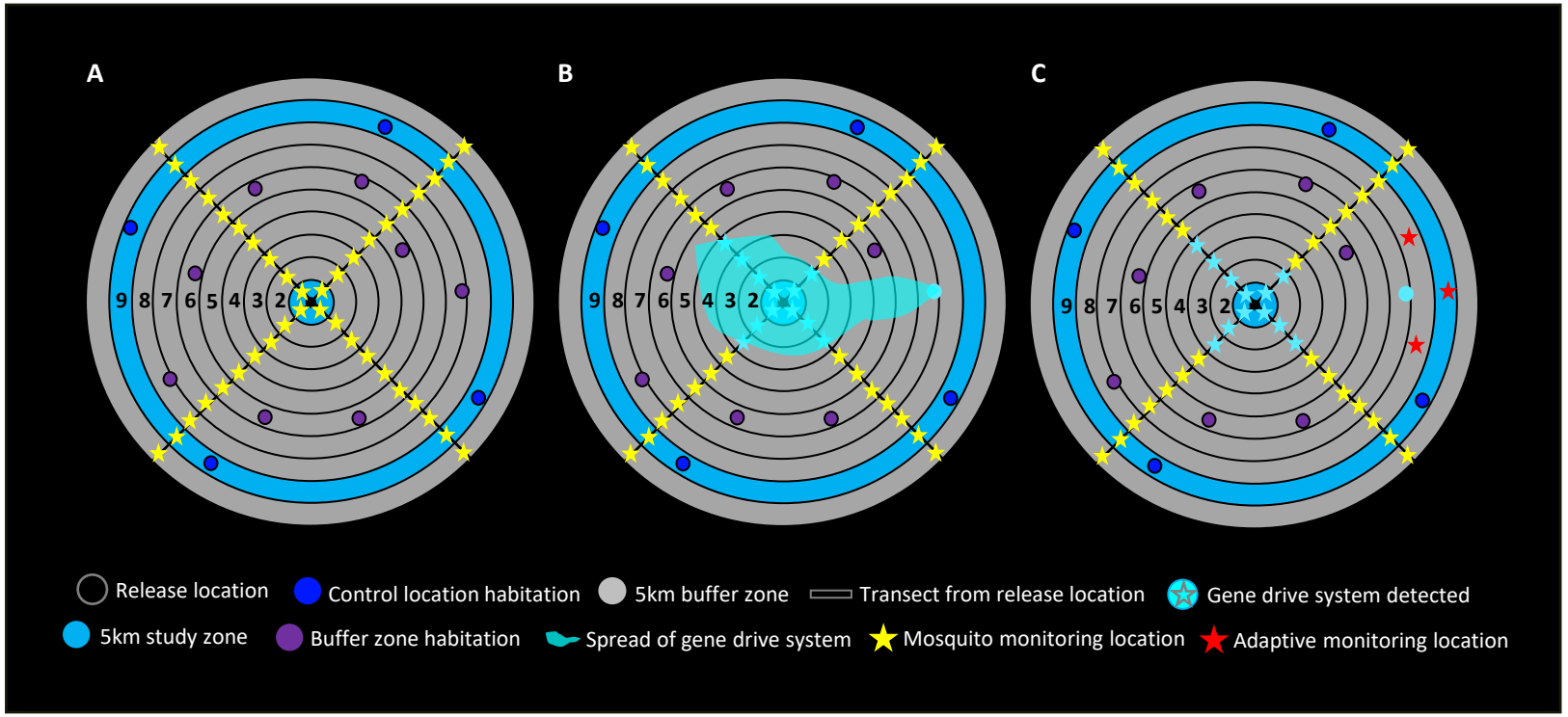
Use of buffer zones to mitigate potential for spillover and adaptive trial design in monitoring of gene drive spread



Options for design of initial low-threshold gene drive field trials to evaluate causal pathway

1

cRCT with randomised release and control locations

- Lack of evidence on genetic efficacy of the gene drive in the field to justify cost of cRCT
- High degree of uncertainty even with modelling on the rate of spread of the gene drive

2

Pilot trial possibly without control locations → cRCT with randomised release and control locations

- Pilot trial to obtain data on spread and dispersal would provide key parameters for iterative modelling final design of cRCT
- Loose opportunity to evaluate epidemiological and entomological impacts from initial releases
- Risk of spillover from initial release locations to trial locations for cRCT means pilot would have to be sufficiently distant to cRCT locations

3

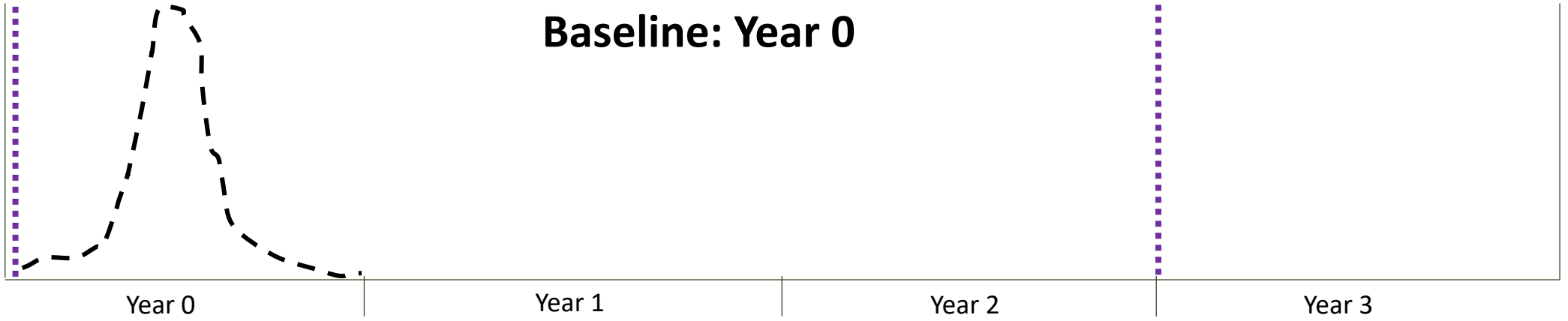
Pilot trial using paired match randomised release and control locations → Sequential addition of paired match randomised release and control locations to achieve power for cRCT

- Pilot trial to obtain data on spread and dispersal in pilot trial would provide key parameters for iterative modelling design of cRCT involving additional paired matched sites, potentially using an adaptive trial design
- Retain opportunity to evaluate epidemiological and entomological impacts from initial releases
- Risk of spillover from initial release locations to additional trial locations can be informed by data on spread from pilot

Pilot trial design

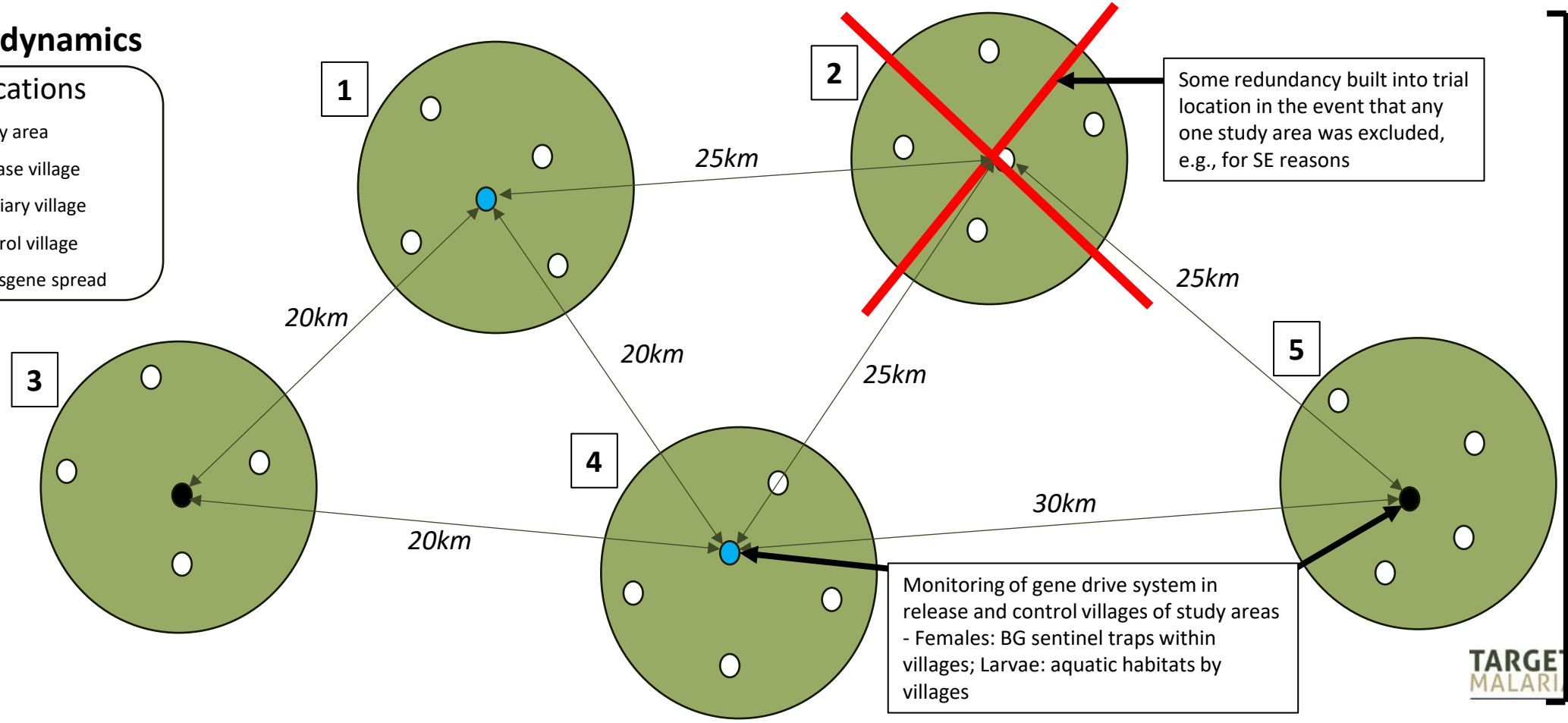
➢Temporal dynamics

Release locations
- Frequency of transgene
- Abundance of transgenics
- Abundance of mosquitoes
- Release of transgenics
- Duration of trial



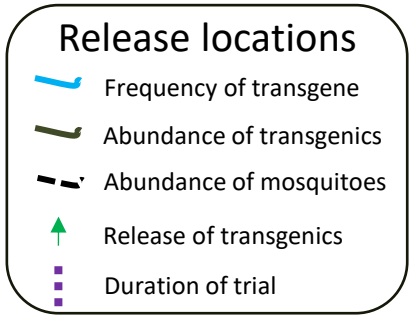
➢Spatial dynamics

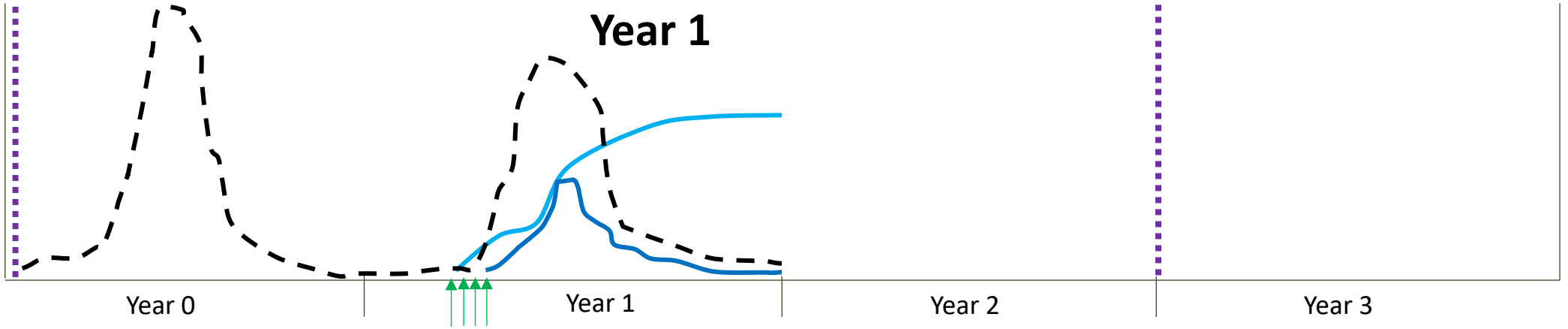
Trial locations
- Study area
- Release village
- Auxiliary village
- Control village
- Transgene spread



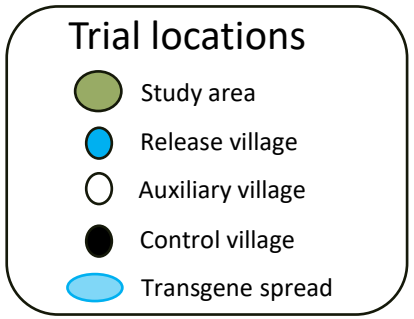
Pilot trial design

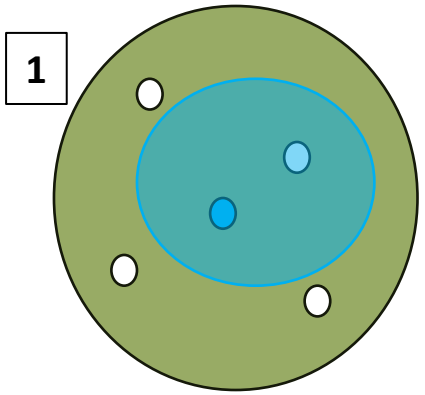
➢Temporal dynamics

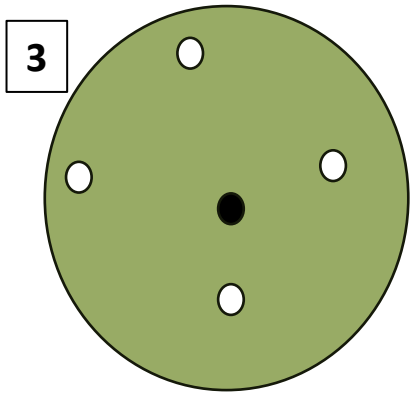


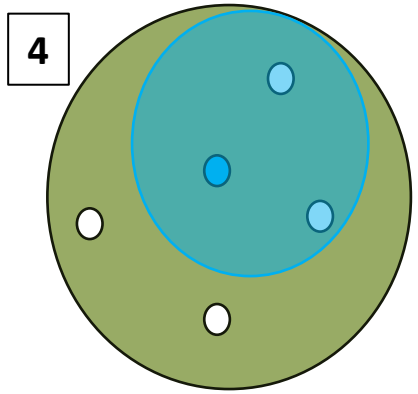


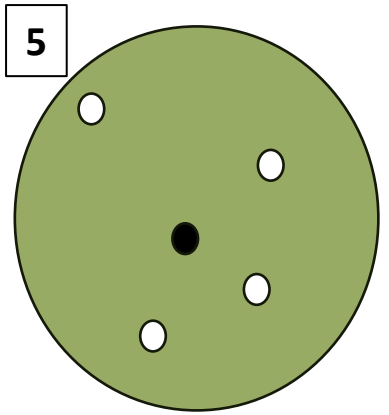
➢Spatial dynamics











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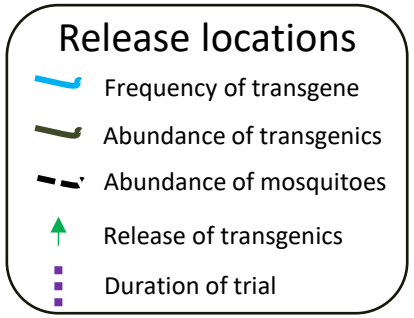
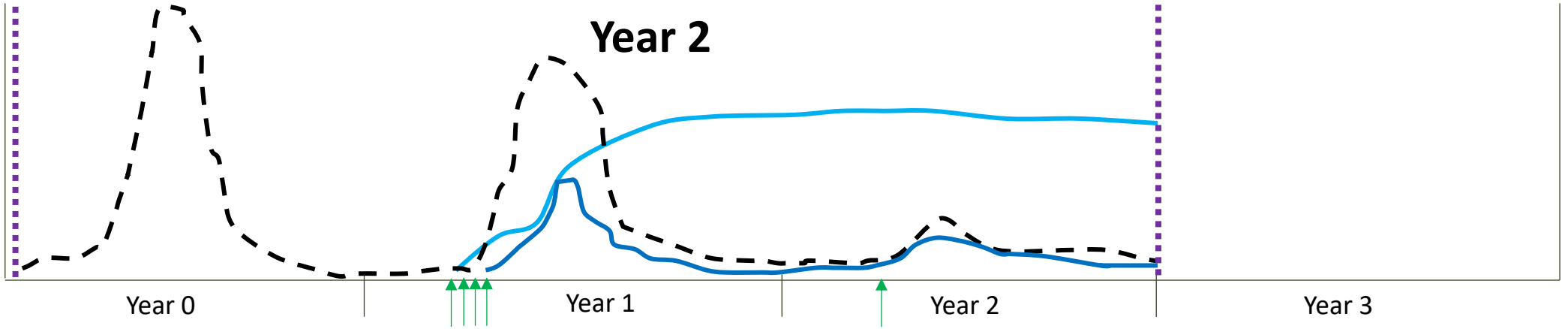
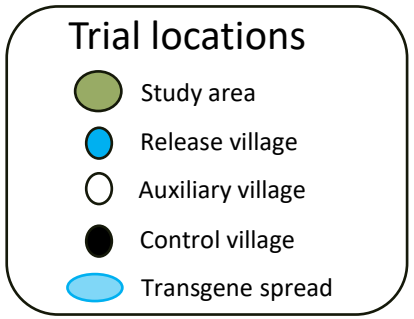
Pilot trial design

➢Temporal dynamics





➢Spatial dynamics



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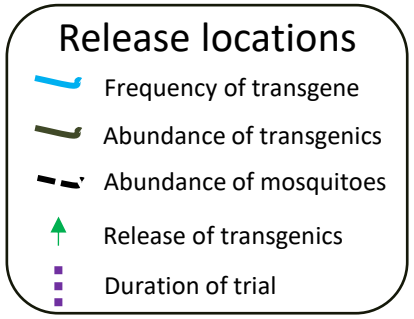
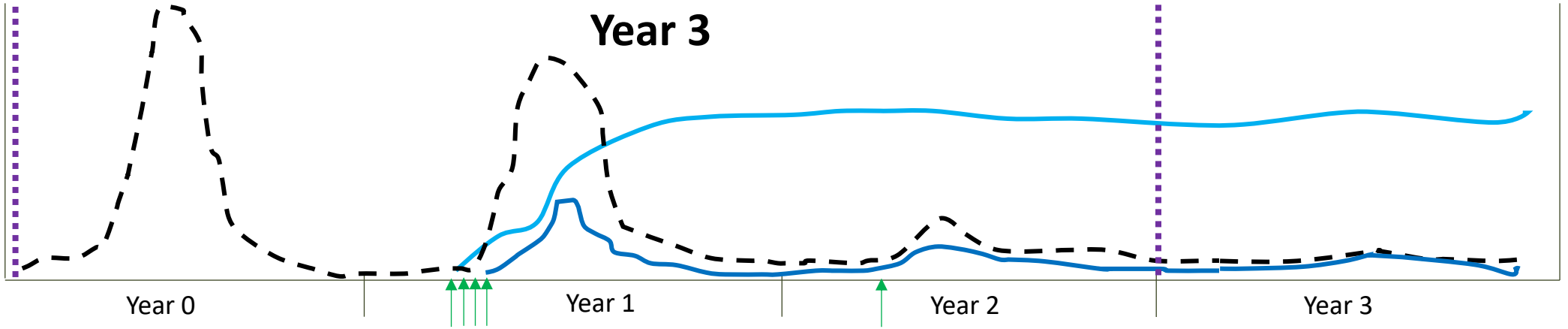
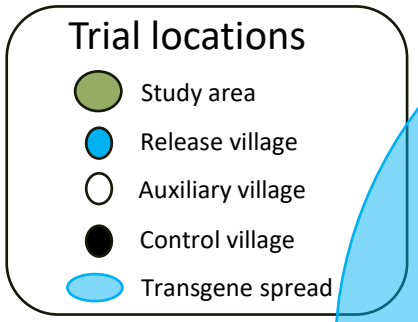
Pilot trial design

➢Temporal dynamics





➢Spatial dynamics



Subsequent to pilot trial, addition of further randomised pair matched locations with less focus on genetic and entomological efficacy and more focus on epidemiological outcomes to achieve statistical power

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Conclusions

1. Low threshold gene drive: potential for indefinite spread and persistence is USP for its implementation for malaria vector control but challenge for design and delivery of initial field trials: however, precedents exist from *Wolbachia* releases and classical biological control

2. First gene drive field trials can be designed around questions to be addressed in causal pathway, as well as outputs from risk assessment, and stakeholder perceptions

3. Utility of buffer zones could accommodate spillover and adaptive trial design could support flexible monitoring and efficacy assessments

4. Potential value in pilot trials to understand spread could be integrated into cRCT that could involve sequential pair match design to evaluate epidemiological, and perhaps entomological impacts, from first releases in the field

5. Progress in product development is advancing ambitions towards field trials of low-threshold gene drive in next five years

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Thank you!

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"Target Malaria receives core funding from the Bill & Melinda Gates Foundation and from Open Philanthropy"

BILL & MELINDA GATES foundation

Open Philanthropy Project

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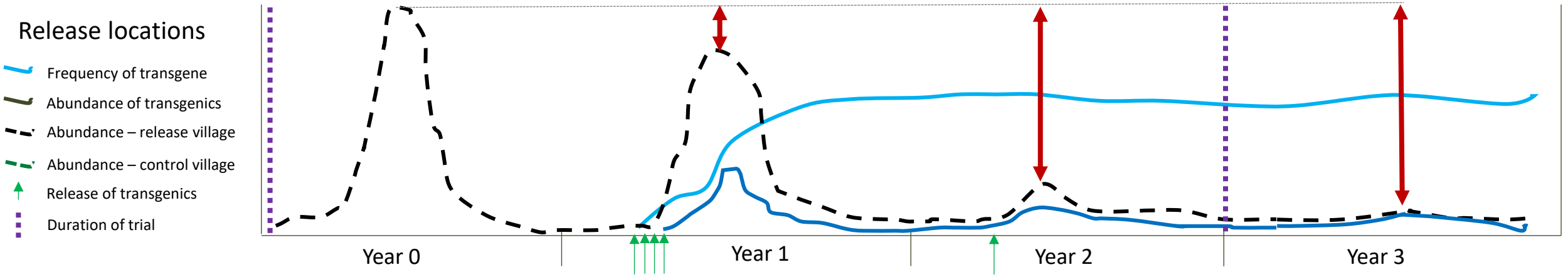
Extra Slides

Analysis	*Broad measurement endpoints*	*Specific research questions*	
		Population suppression	*Population replacement*
Genetic efficacy	A.Extent of increase in frequency of the gene drive system in target mosquito populations. B. Rate of spread from release locations of the gene drive system in target mosquito populations.	• Do the released mosquitoes carrying the gene drive system mate with the target population and is the gene drive system successfully introduced into wild populations? • Does the gene drive system increase in frequency as expected over successive generations? • Is there any evidence of the emergence of alleles that are resistant to gene drive? • What is the rate of spread of the gene drive system in the target population?	
	C. Extent that the gene drive system alters vectorial capacity in mosquito target field populations.	• Is the main phenotype, that females homozygous for the gene drive system are sterile, observable in the field and does this increase in prevalence as the gene drive system increases in frequency?	• Does the main phenotype, that females carrying the gene drive system impede P. falciparum development, increase in prevalence as the gene drive system increases in frequency?
Entomological efficacy	D. Extent that the introduction of the gene drive system coincides with any changes in target mosquito populations or their parasites	• Does the increasing female sterility caused by the gene drive system lead to reduced densities of the target population? • Is there a change in the EIR of the target populations before and after field releases or at release versus control locations? • Is there any evidence of the emergence of alleles that are resistant to population suppression? • Is the gene drive system stable over time?	• Does the diverse genetic background of field-collected mosquitoes affect the expected P. falciparum transmission-blocking phenotype? • Is there a change in the EIR of the target populations before and after field releases or at release versus control locations? • Is there any evidence of the emergence of resistance to the effector gene in P. falciparum or in mosquitoes? • Is the gene drive system stable over time, such that the gene drive remains linked to the functional effector gene?
Epidemiological efficacy	E. Extent that the introduction of the gene drive system coincides with any changes in disease incidence or prevalence	• Is there a change in the incidence or prevalence of malaria before and after field releases or at release versus control locations?	• Is there a change in the prevalence or incidence of malaria before and after field releases or at release versus control locations?
Risk, Entomological efficacy, Epidemiological efficacy,	F. Extent that the risk profile from the releases of the gene drive system is consistent with the outputs of the pre-release ERA.	• Does the gene drive system spread to other sibling species that are sympatric to the released transgenic species and causing adverse impacts? • Is any adverse impact of the gene drive system detected on non-target organisms that impinges health or ecosystem services? • Is any adverse impact of population suppression detected on competitor or predator species that impinges health or ecosystem services? • Is there any evidence of gene flow into, and population suppression of, non-reproductively compatible species of insect?	• Does the gene drive system spread to other sibling species that are sympatric to the released transgenic species and causing adverse impacts? • Is any adverse impact of the gene drive system detected on non-target organisms that impinges health or ecosystem services? • Are there any changes correlated with reduction in P. falciparum in other species of malaria pathogens such as P. vivax, P. ovale, or P. malariae that adversely impacted health or ecosystem services? • Is there any evidence of gene flow into non-reproductively compatible species of insect?
Stakeholders, Epidemiological efficacy	G. Impacts that the field release trials on local or wider stakeholder perspectives to gene drive.	• Do the releases and their impacts change the perspectives of the local or wider communities to the specific intervention and wider technology?	

Impact on densities of target mosquito populations

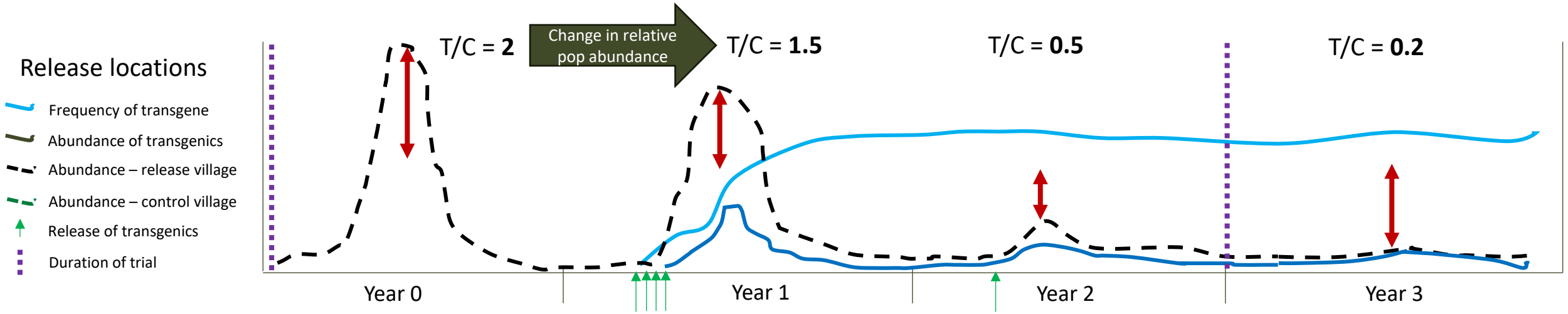
➢Longitudinal

- ○Population abundance vs baseline

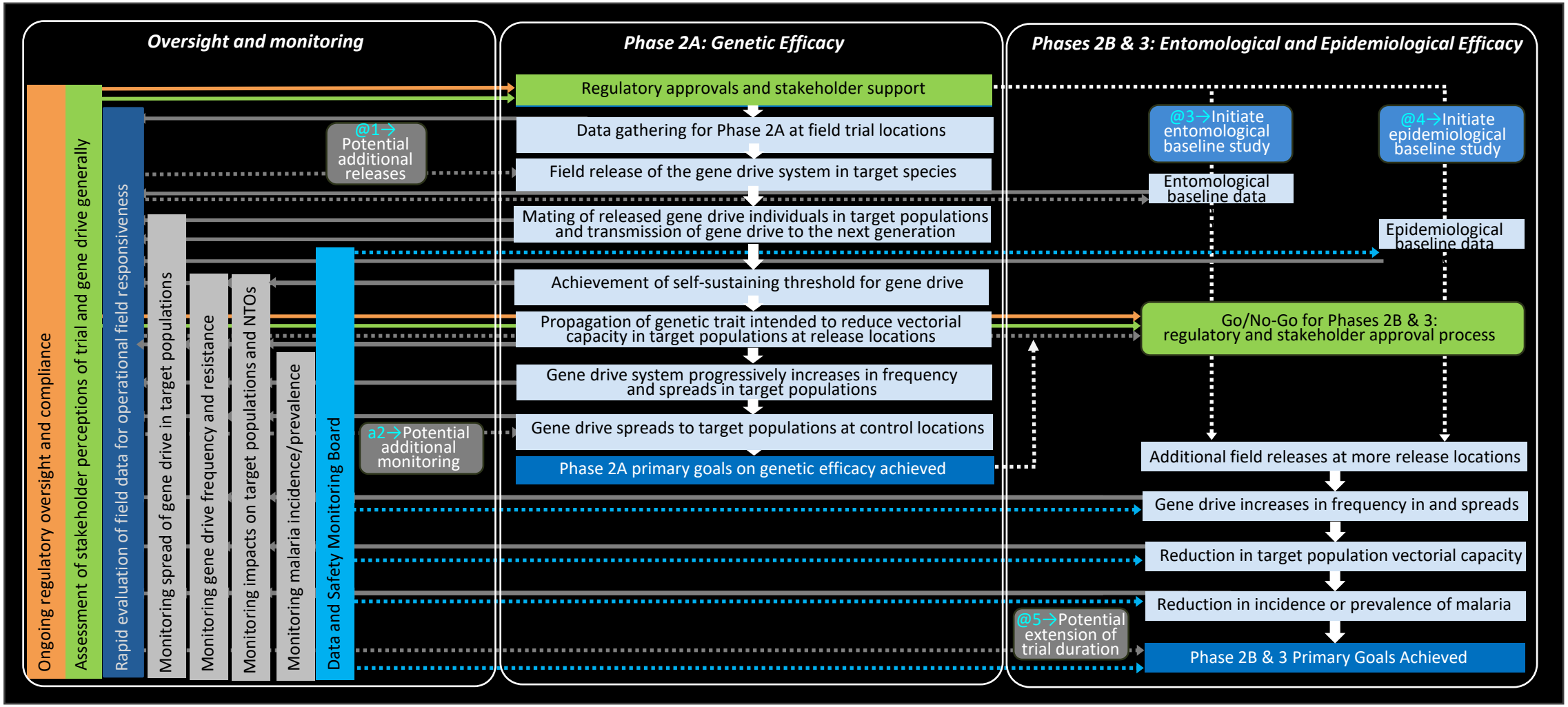


➢Relative to Control

- ○Establish *relative population abundance* at control/release villages during baseline
- ○Assess *change in relative population abundance* before/after treatment
- ○Calibrates for seasonality variability between years



Potential for adaptive trial design and genetic approaches to accommodate stochastic or uncertain gene drive dynamics



Choice of trial location for initial field trials of gene drive

1. **Operational viability:** regulatory structure, public health surveillance, laboratory and insectary access, control sites, safety, familiarity with use of GMOs, stakeholder perceptions

2. **Species composition**: release in a single vector and continuing transmission, introgression via interspecific hybrids

3. **Statistical power**: effect may not be detectable in low transmission areas or overshadowed in high transmission ones, challenges over entomological endpoints and variability

4. **Degree of isolation**: limiting inward and outward migration, islands: coastal or lake islands; private or locally fixed alleles; pre-release ERA and examples from Wolbachia and biocontrol.

5. **Potential for reversibility**: theoretically: resistance strains, anti-drive

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