Title: Phase III, open-label, community-based, cluster randomised controlled trial to evaluate the efficacy, cost-effectiveness, and acceptability of Attractive Targeted Sugar Baits (ATSB) for malaria burden reduction in western Kenya

Short Title: ATSB Study

Trial Identifiers:

KEMRI SERU#: 4189	CDC IRB#: 00008118	LSTM REC#: 21-027	Clinicaltrials.gov

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Funder: Integrated Vector Control Consortium (IVCC), UK, which is funded through a grant by the Bill and Melinda Gates Foundation

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Trial Registration Information: Clinicaltrials.gov <#####>

Trial Sponsor: Liverpool School of Tropical Medicine (LSTM)

Revision Chronology

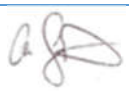
Date	Protocol Version	Details of Changes	Authors	Signature of the PI
31 May 2021	v1.1	Original	AS, EO, JG, ML, JJ, FTK	

TABLE OF CONTENTS

1 ACRONYMS

ACT	Artemisinin-based combination therapy
AE	Adverse event
ANC	Antenatal care
ATSB	Attractive targeted sugar bait
CDC	(US) Centers for Disease Control and Prevention
cMIS	Continuous Malaria Indicator Survey
CRCT	Cluster randomized controlled trial
CS ELISA	Circumsporozoite citrate synthase enzyme-linked immunosorbent assay
DBS	Dried blood spot
DHIS2	District health information system II
DSMB	Data safety monitoring board
EIR	Entomological inoculation rate
GPS	Global positioning system
hCG	Human chorionic gonadotropin
HH	Household
HRP2	Histidine-rich protein-2
FGD	Focus group discussion
ICC	Intracluster correlation coefficient
ICER	Incremental cost-effectiveness ratio
IDI	In-depth interview
IPTp	Intermittent preventative treatment in pregnancy
IRS	Indoor residual spray
IVCC	Innovative Vector Control Consortium
KAP	Knowledge, attitudes, and practices
KEMRI	Kenya Medical Research Institute
LLIN	Long-lasting insecticidal net
LSTM	Liverpool School of Tropical Medicine
MACEPA	Malaria Control and Evaluation Partnership in Africa
MPAC	Malaria Policy and Advocacy Committee
NIH	National Institutes of Health
NIRS	Near-infrared spectroscopy
PCR	Polymerase chain reaction
pLDH	*Plasmodium* lactate dehydrogenase
RDT	Rapid diagnostic test
SAE	Serious adverse event
SEB	Styrene ethylene/butylene styrene
UV	Ultraviolet
VCAG	Vector Control Advisory Group
WHO	World Health Organization

2 ADMINISTRATIVE INFORMATION

2.1 TITLE OF RESEARCH PROPOSAL

Phase III, open-label, community-based, cluster randomised controlled trial to evaluate the efficacy, cost-effectiveness, and acceptability of Attractive Targeted Sugar Baits (ATSB) for malaria burden reduction in western Kenya

2.2 INVESTIGATORS AND COLLABORATORS

2.2.1 Co-Principal investigators

Dr Aaron Samuels [1,3]
Dr Eric Ochomo [2]

2.2.2 Chief Investigator

Prof Feiko ter Kuile [2,3]

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2.2.4 Non-Engaged collaborators

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Dr Kennedy Odhiambo Oruenjo[5]

2.3 INSTITUTIONS

1. Centers for Disease Control and Prevention (CDC)
2. Kenya Medical Research Institute (KEMRI)
3. Liverpool School of Tropical Medicine (LSTM)
4. PATH
5. Siaya County Ministry of Health, Kenya Ministry of Health

2.4 PROTOCOL SUMMARIES

2.4.1 Technical summary

The effectiveness of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) in western Kenya are threatened by insecticide resistance and vector behaviour changes toward early evening and outdoor biting malaria vectors. New tools to control malaria are needed to reduce and even interrupt malaria transmission. Attractive Targeted Sugar Bait (ATSB) is a promising new intervention designed to attract and kill mosquitoes, including those that IRS and LLINs do not effectively target. The ATSB 'bait stations' are A4-sized panels containing thickened fruit syrup laced with a neonicotinoid insecticide (dinotefuran) to attract and kill the foraging vectors. Entomological field trials in western Mali showed that ATSBs successfully reduce mosquito densities and longevity and thus have the potential to reduce malaria transmission. We will conduct a parallel, open-label cluster-randomised controlled trial in 80 village clusters (40 per arm) to evaluate the impact of ATSBs on the burden of malaria. During two years, households in half of these village-clusters will receive two or three ATSB bait stations per household structure on exterior walls approximately 1.8 meters above the ground. ATSBs will be replaced every six months. The primary outcome will be the incidence of clinical malaria in children aged 1-15 years enrolled in a prospective cohort of 5,376 participants followed monthly for about six months each during a 2-year period (2,240 person-years) (this protocol). Secondary outcomes include malaria infection prevalence assessed by rapid diagnostic tests through household surveys and the case burden of clinical malaria assessed by passive facility-based and community-based surveillance (separate protocols). The study includes entomological monitoring and nested acceptability, feasibility and health-economics studies. The stand-alone trial in western Kenya is a part of a multi-country ATSB consortium conducting similar trials in Zambia and Mali.

2.4.2 Lay Summary

Increasing insecticide resistance and changes in the malaria-transmitting mosquitoes' behaviour toward early evening and outdoor biting threatens the effectiveness of the current tools to reduce the malaria-transmitting mosquito. A new tool, the Attractive Targeted Sugar Bait (ATSB), is designed to attract and kill mosquitoes using a sugar attractant laced with insecticide, including those that escape the killing effect of conventional tools, such as indoor spraying with insecticide and insecticide-treated bednets. It reduces the lifespan and density of the malaria-transmitting mosquito population and can reduce malaria transmission when deployed at scale. We will conduct a large trial involving about 80 village-clusters. During a 2-year period, in half of these villages, households will receive two or three ATSB 'bait stations' per household structure every six months to hang outside on their exterior walls. The study aims to reduce the burden of malaria by reducing the number of malaria-infected mosquitoes in the area. This will be assessed by comparing the number of clinical episodes of malaria among 5,376 children aged 1-15 years in the intervention and control villages. The children will be visited at home every month for six months each. The study also includes nested studies assessing the impact ATSBs on mosquito densities and behaviour, acceptability and feasibility studies of ATSB deployment, and assessing the cost-effectiveness of the intervention. The study will take about three years, including about six months to collect baseline data before the ATSBs are used, two years of intervention and six months for data analysis and reporting. Similar studies will be conducted in Zambia and Mali.

2.4.3 Trial Registration data

Data Category	Information		
Primary registry and trial identifying number	Clinicaltrials.gov: [#####]		
Date of registration in primary registry	[#####]		
Secondary identifying numbers	Kenya SERU: 4189	CDC IRB: 00008118	UK LSTM REC: 21-027
Source(s) of monetary or material support	Integrated Vector Control Consortium (IVCC), UK, which is funded through a grant by the Bill and Melinda Gates Foundation		
Primary sponsor	Liverpool School of Tropical Medicine (LSTM); Pembroke Place, Liverpool L3 5QA, UK Phone: +44 0151 7053794; Email: lstmgov@lstmed.ac.uk		
Secondary sponsor(s)	NA		
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Contact for scientific queries	• Aaron Samuels, MD, MHS, Malaria Branch, Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, Kisumu, Kenya and Atlanta, GA, USA. Tel: +254.724.255.633 E-mail: amsamuels@cdc.gov • Dr Eric Ochomo, PhD, Centre for Global Health Research (CGHR), Kenya Medical Research Institute (KEMRI), Kisumu, Kenya. Tel: +254 723 845 457; E-mail: kemricdc.org • Prof Feiko ter Kuile, MD, PhD, Department of Clinical Sciences, Liverpool School of Tropical Medicine (LSTM), United Kingdom. Tel: +44 151 705 3287, E-mail: feiko.terKuile@lstmed.ac.uk		
Public title	Attractive Targeted Sugar Baits (ATSB) for malaria burden reduction in western Kenya: a cluster-randomized trial		
Scientific title	Phase III, open-label, community-based, cluster-randomized controlled trial to evaluate the efficacy, cost-effectiveness, and acceptability of Attractive Targeted Sugar Baits (ATSB) for malaria burden reduction in western Kenya		
Countries of recruitment	Kenya		
Health condition(s) or problem(s) studied	Vector transmission of malaria		
Intervention(s)	Attractive Targeted Sugar Baits (ATSBs)		
Study type	Interventional		
	Allocation: cluster randomized; intervention model: parallel assignment; arms: 2; allocation ratio: 1:1; restricted randomization. Masking: none		
	Primary purpose: Prevention		
	Phase-III		
Date first enrolment	[dd mmm yyyy]		
Target sample size	80 village-clusters, 40 per study arm; cohort 2,400 person-years (1,200 per arm)		
Recruitment status	Not yet recruiting		
Primary Objective	To determine if ATSB deployment plus universal LLIN coverage is superior to universal LLIN coverage alone in reducing the case burden of clinical malaria in western Kenya		

Eligibility criteria	Eligibility criteria for clusters
	• Inclusion criteria clusters
	  ○ A grouping of contiguous rural villages in Alego-Usonga and Rarieda sub-counties of Siaya County
	  ○ A minimum of 200 households
	• Exclusion criteria clusters
	  ○ Hard to reach in the rainy season
	  ○ Refusal to participate by village elders		

Data Category	Information
	Eligibility criteria for participants in the cohort study • Inclusion criteria cohort o A resident of a household within the core area of a study cluster, defined as living in the household in the recent four months and planning to live in the same household for the next 6.5 months o Aged ≥ 1 year and < 15 years at the time of enrollment o Written informed consent and/or assent • Exclusion criteria cohort o A confirmed or suspected pregnancy. Pregnant women are excluded because they are eligible for intermittent preventive treatment of malaria in pregnancy (IPTp). o Taking daily cotrimoxazole prophylaxis (because this has antimalarial effects) o Known sickle cell disease (because they received antimalarial prophylaxis) o Contraindication to artemether-lumefantrine, the medication used for parasite clearance Eligibility criteria for households for ATSB deployment • Inclusion criteria o Households located within one of the 40 clusters (core or buffer area) randomly allocated to the trial intervention arm with a least one permanent resident • Exclusion criteria o Refusal of consent by the head-of-household to deploy ATSB on the outer walls (intervention villages only) o Vacated compounds Eligibility criteria for households for entomological monitoring • Inclusion criteria households for entomological monitoring o Household located within the core area of the cluster o Head of household or his/her representative is at least 18 years of age o Written informed consent for the collection of entomological data by the head of household or representative • Exclusion criteria households for entomological monitoring o No residents sleeping in the household during the planned night of monitoring Eligibility criteria for human landing catches • Inclusion criteria human landing catches o Men aged 18 to 49 years o Willingness and ability to work late at night for up to 7 hours at a time o Willingness to take and tolerate a treatment regimen of the appropriate Kenya Ministry of Health (MoH) recommended antimalarial and chemoprophylaxis with 250 mg of mefloquine weekly to prevent malaria starting two weeks before the start of and until four weeks after completing HLCs o Written informed consent • Exclusion criteria human landing catches o Refusal/inability to work late at night for up to 7 hours at a time o Unwillingness to take or intolerance/allergy to appropriate MoH treatment regimen or chemoprophylaxis Eligibility criteria for participants in rapid ethnographic methods evaluation (community members) • Inclusion criteria ethnographic evaluation (community) o A resident of a household within an intervention area defined as an ATSB area during the main trial or an ASB area during any preliminary studies o Resides in a household at the time of ASB/ATSB deployment, where the ASB/ATSB was installed for at least one month. o 18 years of age or older if participating in focus group discussions; 15 years of age or older if participating in in-depth interviews • Exclusion criteria ethnographic evaluation (community) o Unable to provide consent Eligibility criteria for participants in rapid ethnographic methods evaluation (ATSB monitoring assistants) • Inclusion criteria ethnographic evaluation (ATSB monitoring assistants) o Serving as an ATSB monitoring assistant with experience installing ATSBs and monitoring the deployment

Data Category	Information
	○ Eighteen years of age or older • Exclusion criteria ethnographic evaluation (ATSB monitoring assistants) ○ Less than one month experience (i.e. is new to the job) ○ Unable to provide consent
Primary objective and outcome	
• To determine if ATSB deployment plus universal LLIN coverage is superior to universal LLIN coverage alone in reducing the case burden of clinical malaria in western Kenya	• The incidence rate of clinical malaria by the end of year-2, defined as current fever (axillary temperature of ≥37.5°C) or history of fever in last 48 hours and a positive rapid diagnostic test (RDT, pLDH or HRP2), in children aged 1-<15 years enrolled in the cohort study
Secondary objectives and outcomes	
Efficacy	
• To determine if ATSB deployment plus universal LLIN coverage compared to universal LLIN coverage alone is superior in reducing malaria infection	• The time to first malaria infection assessed by PCR by the end of year-2, in children aged 1-<15 years enrolled in a cohort study • The incidence rate of malaria infection detected by RDT (pLDH) by the end of year-2, in children aged 1-<15 years enrolled in a cohort study • The prevalence of malaria infection diagnosed by RDT in continuous household surveys in participants aged ≥1 month.
• The incidence rate of RDT or microscopy confirmed clinical malaria assessed through passive surveillance at health facilities and community-based surveillance by Community Health Volunteers serving the village-clusters	• The incidence rate of RDT or microscopy confirmed clinical malaria assessed through passive surveillance at health facilities and community-based surveillance by Community Health Volunteers serving the village-clusters
• To determine if the rate of overall illness events differs in the ATSB deployment plus universal LLIN coverage arm when compared to the control arm	• The incidence rate of non-malaria illness in the cohort study • The incidence rate of all-cause sick visits assessed through passive surveillance at health facilities and community-based surveillance by community health volunteers
• To determine if ATSB deployment plus universal LLIN coverage compared to universal LLIN coverage alone reduces malaria transmission or affects insecticide resistance	• Entomological outcomes including malaria vector densities, the proportion of females older than three gonotrophic cycles, sporozoite rate, EIR and markers of insecticide resistance • Antibodies against merozoite surface protein-1 (MSP-1), circumsporozoite proteins (CSP) and other malaria antigens • Molecular measurements including, but not limited to, 24-single-nucleotide polymorphisms (24-SNP) barcodes for the complexity of infection • Mosquito salivary antigens for biting rates
Safety	
• Assess the safety of ATSBs on humans	• Adverse events associated with Adverse events associated with misuse or loss of ATSBs.
• Assess the safety of ATSBs on non-target insects	• Continued entomological monitoring of non-target insect populations
Ethnographic evaluation	
• To understand the acceptability and potential factors that influence ATSB coverage	• The proportion of ATSBs that have been moved/removed • The proportion of household heads who perceive ATSBs as safe and effective
• Assess the acceptability of ATSBs by communities and other stakeholders	• Identification of potential barriers to uptake and consistent ATSB coverage, • Assessment of the impact of ATSBs on the coverage and use of existing malaria control interventions (e.g. LLIN, IRS, treatment-seeking behaviour)
Health economics	
• Estimate the cost-effectiveness of deploying ATSBs for malaria control.	• Incremental cost-effectiveness of ATSB above the standard of care measured through costing of intervention and efficacy outcomes

3 INTRODUCTION

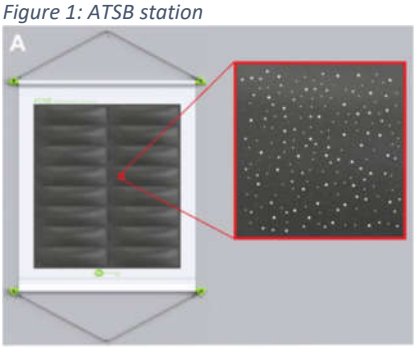
3.1 ATSB BACKGROUND AND LITERATURE REVIEW

The current malaria vector control tools, long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) are critically important and have saved many lives [1]. However, their effectiveness in western Kenya is threatened by insecticide resistance and vector behaviour changes toward more early evening and outdoor biting malaria vectors. LLINs and IRS specifically target indoor-biting and indoor-resting mosquitoes. Malaria vectors exhibit different behavioural characteristics that mitigate the effectiveness of vector control strategies. For example, traditionally, *An. gambiae s.s.* has been regarded as human-biting with late-night indoor-feeding and indoor-resting behaviours, while *An. Arabiensi* is found more often in drier environments and is more zoophagic with outdoor biting and resting behaviours. Following LLINs and IRS's widespread scale-up, the dominant African vectors' distributions and behaviours changed with *An. gambiae s.s.* and *An. Funestus* (also an indoor human biter) diminishing in abundance relative to *An. arabiensis* [2]. Subsequently, shifts towards earlier evening biting by *An. Gambiae* s.s. (before people enter houses to sleep under LLINs) and later biting by *An. Funestus* (biting in the morning after sunrise [3, 4]) are examples of behavioural plasticity enabling these species to avoid contact with the LLIN and IRS insecticides.

There is a need for interventions that supplement and complement LLINs and IRS by killing mosquitoes outside houses using other biologic mechanisms (e.g., targeting sugar feeding behaviour). [5-7]. Furthermore, insecticides are required with novel modes of action that may restore sensitivity to pyrethroids by killing both pyrethroid-resistant and sensitive mosquitoes.

Attractive Targeted Sugar Bait (ATSB) (the name was recently changed from Attractive Toxic Sugar Bait to highlight that it targets malaria vectors) is a promising new intervention that potentially fills the need for outdoor interventions with novel killing effects. ATSB 'bait stations' are A4-sized panels containing thickened fruit syrup laced with a neonicotinoid insecticide (dinotefuran) to attract and kill the foraging vectors. Entomological field trials in Mali showed that ATSBs successfully reduce mosquito densities and longevity and thus have the potential to reduce malaria transmission [8].

Figure 1: ATSB station



Large scale efficacy studies are now needed to establish the efficacy of ATSB for controlling malaria transmission. We will propose a parallel, open-label cluster-randomized controlled trial in 80 village clusters (40 per arm) to evaluate the impact of ATSBs on the burden of malaria in western Kenya, where sustained malaria transmission occurs despite the scale-up of LLINs or IRS.

3.2 ADDRESSING RESIDUAL OUTDOOR MALARIA TRANSMISSION

LLINs and IRS are not well-suited for malaria vectors that avoid contact with indoor insecticides, frequently bite animals, and rest outdoors or remain within houses only briefly when they enter [5, 6]. These behaviours allow residual populations of vector mosquitoes to survive, expand, and increasingly contribute to malaria transmission, despite high LLIN and IRS coverage [6]. These vectors can sustain endemic transmission even if they rarely bite humans. *An. arabiensis* is a

particularly important source of persistent residual transmission. This mosquito prefers to feed on animals, often bites and rests outside, and has limited indoor exposure [5, 6].

In addition to the biological need for female *Anopheles* species to take a blood meal to obtain protein necessary for egg production, both male and female *Anopheles* must feed regularly on liquid and carbohydrates (sugars) to survive. Common sources of liquid and sugar meals include plant tissue and floral nectar. Mosquitoes are guided to sugar sources by chemical attractants. ATSBs are designed to attract the mosquito with a source of liquid and sugar. Because the sugar is laced with a toxicant, it kills the mosquito when ingested [9]. A limited number of studies have shown that using sugar sources to attract mosquitoes to an ingestion toxicant is a relatively simple and inexpensive strategy for mosquito control [10], even in sugar-rich environments [11].

Early studies examined the effect of spraying ingestion toxicants on attractive flowers to use their scent as bait. While these flowers effectively attract the target mosquitoes, the impact on non-target insects, especially pollinators, can be devastating. Furthermore, this approach is not suitable in areas with a lack of flowering vegetation [9].

3.3 ATSBs

Westham Co., based in Israel, recently developed a bait station containing a fruit syrup to attract mosquitoes, sugar to stimulate feeding, and an active ingredient (the neonicotinoid, dinotefuran) to kill the foraging vectors. The bait station contains a commonly used bittering agent called Bitrex (https://www.bitrex.com/en-us) that deters human and animal consumption of the bait. The bait stations also contain a pH regulator (citric acid), preservative (sodium benzoate), and thickener (xanthan gum). They have a protective membrane that covers and protects the bait from rain and dust but allows mosquitoes to feed through it (See Figure 1: ATSB station, page 12). The protective membrane will enable mosquitoes to feed, but it serves as a barrier to non-target organisms. Field studies to-date have also shown that the ATSB has a minimal impact on non-target organisms (NTOs) and humans. This includes evidence specifically for the toxicant that will be used, dinotefuran [12]. The Westham ATSB can remain effective in the field for at least six months and has a shelf life greater than three years with no specific storage requirements. This ATSB is now being produced at an industrial scale, uses simple and widely available ingredients, and limits environmental contamination with insecticides.

ATSBs may be an essential vector control tool in the context of insecticide resistance. Insecticide resistance for the six insecticide classes currently used in LLINs and IRS threatens malaria prevention efforts. Resistance to pyrethroids (used in LLINs and IRS) is commonly reported (http://www.irmapper.com). If pyrethroids lose most of their efficacy, more than 55% of vector control benefits could be lost [13]. ATSBs can help mitigate insecticide resistance to these contact insecticides because they can use ingestion toxicants from very different chemical classes. Many existing ingestion toxicants may be used in a bait station, facilitating resistance management strategies, such as rotation or combination approaches.

3.4 Field experience with ATSB in Mali

Proof of concept studies from Mali demonstrated that the ATSBs had the desired impact on mosquito vector populations [8]. Outdoor use of ATSBs was found to reduce vector abundance by 57.4%, and the older mosquito population surviving long enough to transmit malaria by 97.1-100%. Preventing *Anopheles* mosquitoes from living long enough for the ingested malaria gametocytes to mature to sporozoites is key to preventing onward transmission. The studies in Mali also established

an optimal deployment pattern. They showed that two ATSBs installed on opposite exterior walls of sleeping structures at a height of 1.8 meters were associated with a target mosquito feeding rate of at least 30% and a >90% reduction in vector populations [8].

3.5 Field experience with ATSB in western Kenya

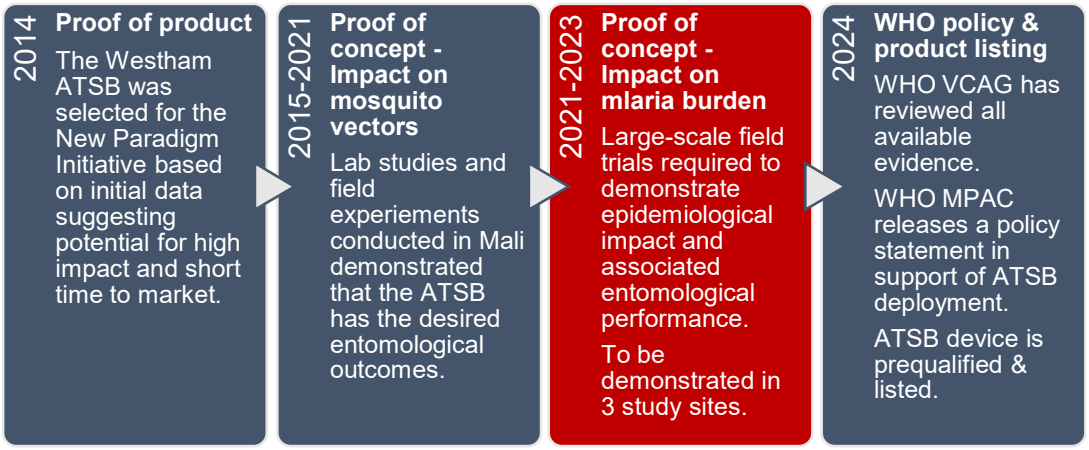
In western Kenya, similar entomological validation studies are ongoing under a separate protocol (SSC-3613; CDC IRB # 7112; LSTM REC # 18.015).

The initial entomological validation trial in Kenya was carried out between Nov 2020 and Jan 2021 with Attractive Sugar Bait stations (ASBs), which are like ATSB but without the toxin and contain a fluorescent dye. Preliminary results indicate that three ASBs hung on the exterior walls resulted in cumulative mosquito feeding rates of up to 30 % among *An. gambiae* and 60% among *An. funestus* during the first month of ASB deployment. The estimated *daily* feeding rate was 7% for *An. gambiae* and 11% for *An. funestus*, which for both species is above the 2.5% threshold estimated by mathematical models to result in a 30% reduction in malaria incidence.

Additionally, the team assessed natural sugar feeding rates for these malaria vectors and found the average rate was 38% and 27% among *An. funestus* male and female mosquitoes, respectively, and 26% and 13% among male and female *An. gambiae* mosquitoes, respectively. A larger pilot study (SSC-3613; CDC IRB # 7112; LSTM REC # 18.015) is planned for May-June of 2021, comparing feeding rates when deploying two versus three bait stations per structure. The information will be used to inform the final number of bait stations required in the larger efficacy trial described in the current protocol.

4 Justification for the study

Figure 2: Timeline for the ATSB New Paradigm Initiative 2014–2024



Malaria prevention tools currently deployed at scale have been highly effective in reducing malaria, but in high transmission areas, these are insufficient to further reduce and ultimately interrupt transmission. The ATSB is a new tool designed to attract and kill mosquitoes, including those that IRS and LLINs do not effectively target. Modelling studies suggest that ATSBs could significantly reduce mosquito populations across a range of different transmission intensities and have great potential to further reduce malaria transmission in areas with high uptake of indoor vector control tools (e.g. LLINS and/or IRS) [7, 14]. To accelerate the evaluation of ATSBs as a potential public health strategy,

larger scale and multi-site studies are now needed to assess the impact on malaria infection and transmission outcomes (Figure 2).

The results of this study will be submitted to the WHO Vector Control Advisory Group (VCAG), the advisory body to the WHO on new vector control classes for malaria and other vector-borne diseases. VCAG will review the ATSB public health value iteratively and provide regular updates to the Malaria Policy Advisory Committee (MPAC). MPAC will provide a recommendation to WHO based on available evidence. WHO will then formulate the recommendation and operational guidance for the product, and subsequent products in this product class will be eligible for WHO prequalification listing [15]. Many countries and donors will not purchase or import products that do not have a listing.

5 OBJECTIVES AND OUTCOMES

Table 1: Objectives and outcomes

5.1 PRIMARY OBJECTIVE AND OUTCOME

Primary objective	**Primary endpoint**
To determine if ATSB deployment plus universal LLIN coverage is superior to universal LLIN coverage alone in reducing the case burden of clinical malaria in western Kenya	• The incidence rate of clinical malaria by the end of year-2, defined as current fever (axillary temperature of ≥37.5°C) or history of fever in last 48 hours and a positive rapid diagnostic test (RDT, pLDH or HRP2), in children aged 1-<15 years enrolled in the cohort study

5.2 SECONDARY OBJECTIVES AND OUTCOMES

5.2.1 Efficacy

Secondary objectives	**Secondary endpoints**
To determine if ATSB deployment plus universal LLIN coverage compared to universal LLIN coverage alone is superior in reducing malaria infection	• The time to first malaria infection assessed by PCR by the end of year-2, in children aged 1-<15 years enrolled in a cohort study • The incidence rate of malaria infection detected by RDT (pLDH) by the end of year-2, in children aged 1-<15 years enrolled in a cohort study • The prevalence of malaria infection diagnosed by RDT in continuous household surveys in participants aged ≥1 month.
To determine in ATSB deployment plus universal LLIN coverage compared to universal LLIN coverage alone reduces the clinical case burden in health facilities and communities	• The incidence rate of RDT or microscopy confirmed clinical malaria assessed through passive surveillance at health facilities and community-based surveillance by Community Health Volunteers serving the village-clusters

To determine if the rate of overall illness events differs in the ATSB deployment plus universal LLIN coverage arm when compared to the control arm	• The incidence rate of non-malaria illness in the cohort study • The incidence rate of all-cause sick visits assessed through passive surveillance at health facilities and community-based surveillance by community health volunteers
To determine if ATSB deployment plus universal LLIN coverage compared to universal LLIN coverage alone reduces malaria transmission or affects insecticide resistance	• Entomological outcomes including malaria vector densities, the proportion of females older than three gonotrophic cycles, sporozoite rate, EIR and markers of insecticide resistance • Antibodies against merozoite surface protein-1 (MSP-1), circumsporozoite proteins (CSP) and other malaria antigens • Molecular measurements including, but not limited to, 24-single-nucleotide polymorphisms (24-SNP) barcodes for the complexity of infection • Mosquito salivary antigens for biting rates
5.2.2 Safety	
Assess the safety of ATSBs on humans	• Adverse events associated with misuse or loss of ATSBs.
Assess the safety of ATSBs on non-target insects	• Continued entomological monitoring of non-target insect populations
5.2.3 Ethnographic evaluation	
To understand the acceptability and potential factors that influence ATSB coverage	• The proportion of ATSBs that have been moved/removed • The proportion of household heads who perceive ATSBs as safe and effective
Assess the acceptability of ATSBs by communities and other stakeholders	• Identification of potential barriers to uptake and consistent ATSB coverage, • Assessment of the impact of ATSBs on the coverage and use of existing malaria control interventions (e.g. LLIN, IRS, treatment-seeking behaviour)
5.2.4 Health economics	
Estimate the cost-effectiveness of deploying ATSBs for malaria control.	• Incremental cost-effectiveness of ATSB above the standard of care measured through costing of intervention and efficacy outcomes

6 TRIAL DESIGN AND DESIGN CONSIDERATIONS

6.1 OVERVIEW OF STUDY DESIGN

This will be a phase III, open-label two-arm cluster randomized controlled superiority trial (CRCT) with a 1:1 allocation ratio to compare ATSB + LLINs vs LLINs alone (standard of care).

During the baseline year, 100 clusters will be followed for 1-year. Clusters consist of approximately 1 to 3 contiguous villages to achieve an optimal cluster size of between 200-400 households per cluster. Clusters are divided into core and buffer areas, as described in Section 6.2.3, Measures to avoid contamination, page 17. The sampling frame for measuring baseline and main study outcomes will be restricted to permanent residents residing in households within each cluster's core area to reduce contamination. After the baseline period, 80 out of the 100 clusters will be allocated to one of the two arms using restricted randomization based on the optimal combination of options that minimizes imbalance in baseline predictors between study arms.

The study is designed to detect a ≥30% reduction in the primary outcome over two years, which is the incidence of clinical malaria in a cohort of children aged 1-15 years, defined as current fever (axillary temperature of ≥37.5^{o}C) or history of a fever in the last 48 hours and a positive RDT. The WHO considers this effect size to be the minimal reduction required worthy of a WHO recommendation. The prevalence surveys will also be powered to detect a 30% reduction in malaria prevalence by RDT each year.

6.2 Design Considerations

6.2.1 Superiority trial to detect at least a 30% reduction

The study is designed as a superiority trial to detect at least a 30% reduction compared to the current standard of care (universal coverage of LLINs) over a two-year period, which is the minimum reduction considered worthy of a WHO recommendation and large-scale deployment.

6.2.2 Duration of trial, interim analysis and criteria for early termination

This study in Kenya is part of three similar trials conducted in Kenya (this protocol), Zambia and Mali. The purpose of these trials is to inform the assessment of public health value by WHO's Vector Control Advisory Group (VCAG). This requires at least a single year of data, but ideally, two years [16-18]. This trial in Kenya is designed to have two interim and one final analysis, i.e. a total of three looks. The main purpose of these interim analyses is to inform WHO's recommendation making process in a timely manner. In brief, the interim analyses will occur either after 50% and 75% of person-time have completed (i.e., after about 1 and 1.5 years respectively), or after 50% (n=372) and 75% (n=558) of the total number of expected primary outcome events over two years in the control arm (n=744) have occurred (whichever comes first). The number of events will be tracked by an independent statistician not involved in the trial. Whether the interim analysis results will lead to the early stoppage of this trial, e.g., for futility or overwhelming evidence of efficacy, will depend on the overall evidence from the three trials. Please see Section 9.4.1, Interim analysis, page 44, for details of the interim analysis's purpose and procedures.

6.2.3 Measures to avoid contamination

Contamination or spillover effects between study arms may bias results towards the null. Therefore, the study will use a "fried egg" design. In interventions clusters, ATSBs will be deployed throughout the entire cluster. However, the effect will only be obtained from households located in the core of the cluster. Excluding measurement for the primary outcome in buffer zones will ensure that households in control villages are excluded that may benefit from a community effect from proximal households in neighbouring intervention villages.

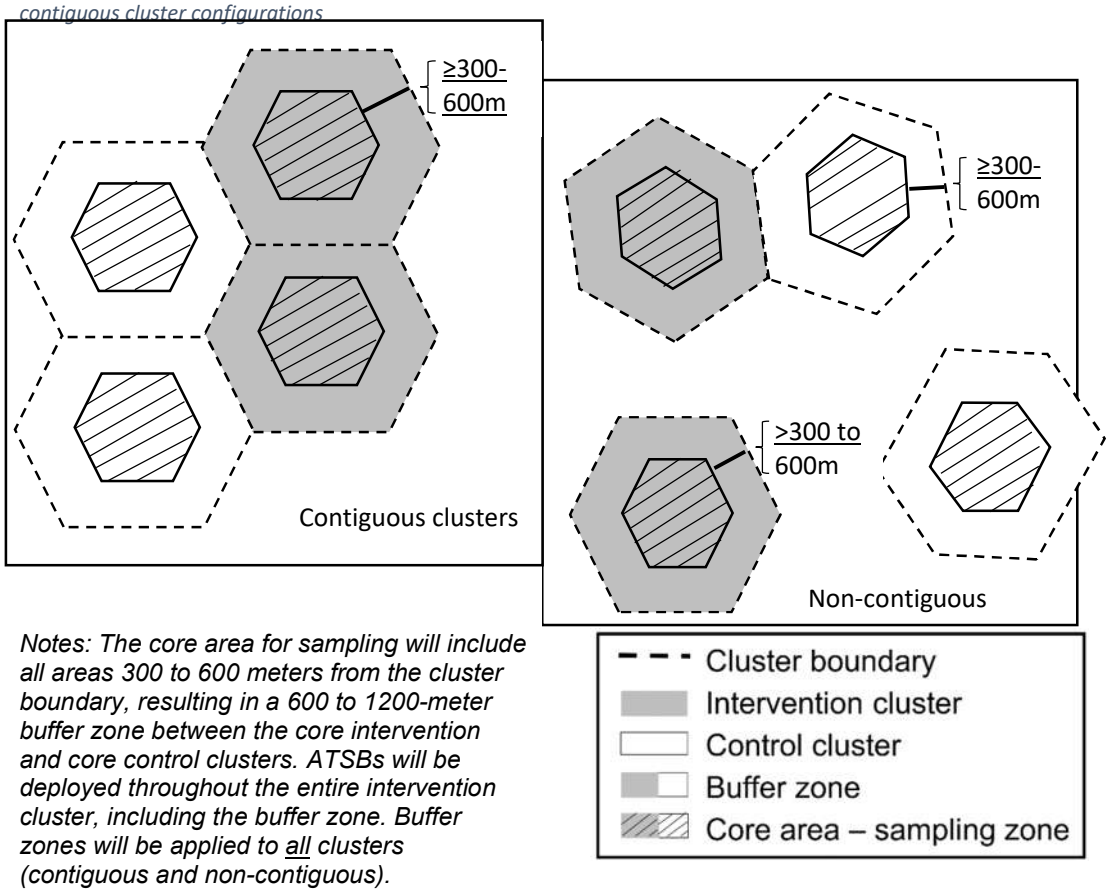
The core area is defined as an area that is at least 300 to 600 meters from the perimeter of the cluster (i.e. at least 600 to 1200 meters between core areas of contiguous clusters), based on findings on the design of a recent cluster-randomized trial in Tanzania [19].

The buffer zones will be uniformly applied to each study cluster, including control clusters that do not border an intervention cluster or vice versa. This will be done to avoid the potential confounding factor of household distance from the cluster centre. For example, cluster borders may consist of a river or stream. The presence of water may result in a relatively higher or lower risk of malaria infection exposure compared to the core area, or the household density may differ between core and buffer areas, etc.

The boundaries for the core and buffer areas are based on recent mapping and census data.

Only the analysis of the data from the cohort study (primary outcome), parasite prevalence survey, and entomological monitoring will use the "fried egg" approach. The analysis of the passive facility-based or community-based surveillance data cannot use the fried-egg approach because only data on the village of residence, and not the geo-location of a household, is available in the routine clinical or CHV registers.

Figure 3: Buffer zone and core zone for sampling within each study cluster at trial sites with contiguous and non-contiguous cluster configurations



Notes: The core area for sampling will include all areas 300 to 600 meters from the cluster boundary, resulting in a 600 to 1200-meter buffer zone between the core intervention and core control clusters. ATSBs will be deployed throughout the entire intervention cluster, including the buffer zone. Buffer zones will be applied to all clusters (contiguous and non-contiguous).

6.2.4 Assessment of community effects.

Should funds permit, additional participants from the buffer zones may be enrolled in the cohort study or continuous household surveys to examine the community effect, i.e. the degree to which intervention effects wane by distance and/or spill over into neighbouring control clusters. See Section 7.8, Sample size, page 30, for further details on sample size and sampling.

6.3 OVERVIEW OF ACTIVITIES AND PROCEDURES

The following list provides a general overview of planned research activities, with a full description included in Section 9, Methods: Data collection, management and analysis, pages 34 to 42. Please refer to Figure 4: Overview of activities and procedures in intervention and control areas, page 20, for a graphical overview of activities and to Table 8: Timeline, page 62, for a timeline of the planned activities.

6.3.1 Creation of clusters

Clusters have been created using data from a recent mapping and census exercise conducted in the study areas (Rarieda and Alego-Usonga sub-Counties of Siaya County). A total of 100 clusters were created from either a single village or multiple combined villages to achieve an optimal cluster size ranging between 200–400 households per cluster. Within each cluster, a core and buffer area have been delineated (see Section 6.2.3, Measures to avoid contamination, page 17). Additionally, these data are used to inform the denominator for the measurement of the incidence from passive case detection.

6.3.2 Baseline data collection

The baseline malaria incidence, prevalence, and contextual data will be collected in a cohort study (6.3.3.1, below) and household survey (6.3.3.3, below) conducted in 100 clusters prior to ATSB deployment. This data will be used to inform the restricted randomization and select the 80 clusters for inclusion in the main trial. The incidence and prevalence data will also be used to confirm the necessary sample size for the cohort and household survey required for the main trial to assess impact. Baseline entomological data (including mosquito age structure, mosquito density, sporozoite rates, insecticide resistance, and EIR) will be collected in 30 randomly selected clusters to inform the restricted randomization.

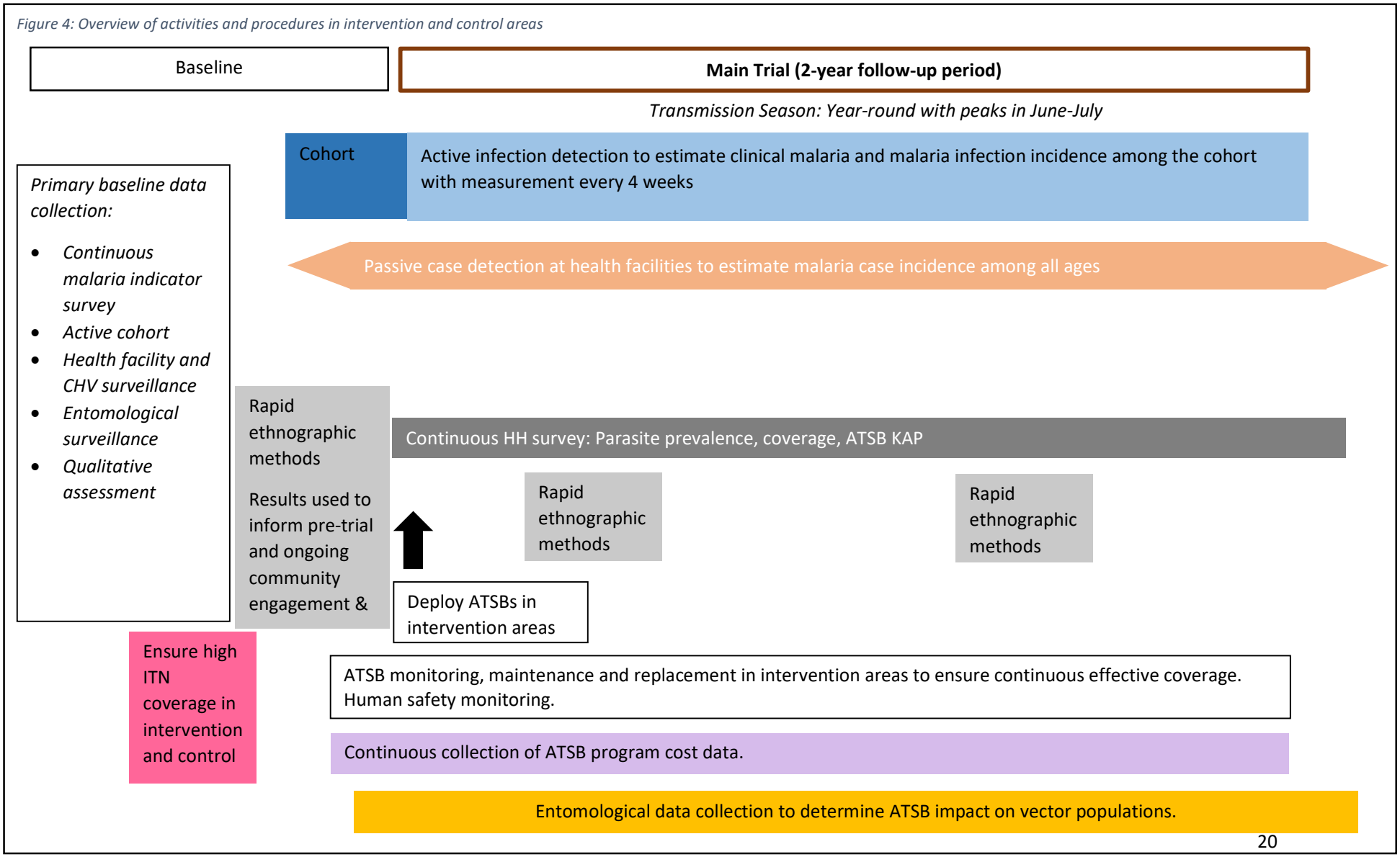
6.3.3 Epidemiological data

The epidemiological data sources for both the baseline and the main trial will include:

6.3.3.1 *Cohort study (active case detection)*

Participants aged 1 to <15 years who are usual residents of households within a core area of a study cluster will be randomly selected for enrolment into an active cohort (see section 9.1.2, Cohort study to assess the incidence of clinical malaria, page 34). All consented and enrolled cohort members will be given a presumptive treatment course of artemether-lumefantrine to clear any malaria infections. Parasite clearance will be confirmed two weeks after treatment. The scheduled monthly cohort visits will begin one month after the first day of this treatment. During monthly visits, study staff will collect a fingerprick (or heel prick in small infants) blood sample (about 250uL to 1 ml) for dried blood spots on filter paper. Should the cohort member report a fever in the last 48 hours or have an axillary temperature of ≥37.5°C at the time of the visit, the study staff member will perform a malaria RDT, and if positive, will treat the participant as per the Kenya Ministry of Health guidelines. A questionnaire will be administered to all cohort members and/or their caregivers to assess for illness, care-seeking, and LLIN usage, among other indicators. Several questions will be asked to monitor for any SAEs. A questionnaire assessing ATSB knowledge, attitudes and perceptions (KAP) will also be administered. Please see section 9.1.7, Rapid ethnographic methods, page 39, for more details.

Figure 4: Overview of activities and procedures in intervention and control areas



6.3.3.2 *Passive surveillance of case burden (health facility and community-based surveillance)*

Data to estimate the all-age malaria case burden will be obtained using routine data collected in the Kenya Ministry of Health registers from outpatient health facilities, antenatal clinics, and CHVs serving the clusters' catchment areas. In brief, de-identified data are captured from the facility and CHV registers (paper-based register books). Village of residence data are collected in these registers and will be used to classify participants as coming from intervention or control clusters or outside the study area. Census data will be used to calculate the initial cluster population denominators. Census data collected by the CHVs annually may be used to update cluster denominators and sampling frames. Please see Section 9.1.4, Passive case detection, page 37, for more details.

6.3.3.3 *Continuous malaria indicator household surveys (cMIS)*

Malaria prevalence data will be obtained from ongoing continuous (year-round) malaria indicator surveys (cMIS) under an existing protocol (SSC 2773; LSTM Protocol 14.009; CDC Protocol 6733). As part of these surveys, fingerprick blood samples are collected for malaria RDTs and dried blood spots for later molecular and serological testing. Participants testing RDT positive are treated according to the Kenya Ministry of Health guidelines. A questionnaire is administered to the selected individual or their caretaker to evaluate key contextual variables, including human behavioural factors, demographic characteristics, and travel patterns. Please see Section 9.1.3, Continuous household survey, page 36 for more details.

6.3.4 Rapid ethnographic methods

Qualitative research methods will be applied early in the study, including in-depth interviews (IDI) and focus group discussions (FGD) to assess community perceptions and attitudes regarding ATSB deployment. Initial qualitative work will inform the development of community engagement and communications plans. This work will be undertaken prior to the initial deployment of ATSBs. Subsequent work after ATSB deployment will examine knowledge, attitudes, and practices. Changes in communication strategies may be needed to ensure full coverage and adherence. Please see section 9.1.7, Rapid ethnographic methods, page 39, for more details.

6.3.5 Sensitization of the population

Meetings will be held with the County and sub-County Health Management Teams and in the study villages to explain the interventions, the purpose of the study, and the need for randomizing communities to one of the two study arms.

6.3.6 LLIN distribution

A Government of Kenya sponsored mass LLIN distribution campaign occurred in April 2021 within the study area to achieve universal access to LLINs (1 LLIN per 2 household members). Using data from the baseline cMIS survey, we will measure LLIN coverage and attrition prior to the main trial and perform top-up distributions in all clusters as warranted.

6.3.7 ATSB deployment and monitoring and maintenance

6.3.7.1 *Deployment*

ATSBs will be deployed according to the optimal protocol identified during the entomological validation studies. The deployment protocol will entail installing two or three bait stations per structure on exterior walls approximately 1.8 meters above the ground or as high as possible on shorter walls. Community-based staff will install the ATSBs according to manufacturer instructions. Consent will be obtained from both community leaders within selected clusters and individual heads of household. At the time of deployment, household owners will be educated on the importance of

ensuring that the ATSBs remain on the exterior walls for the validity of the study and to avoid potential adverse effects on humans. Household owners will be instructed to contact study staff if ATSBs are damaged or lost to allow for replacement.

6.3.7.2 *Continuous monitoring and maintenance of ATSBs*

A monitoring component will ensure that ATSB coverage remains high for the duration of the study. Community-based monitoring assistants will monitor all or a sample of bait stations about once per month and capture data on placement and condition. The bait stations will be replaced as required or every six months (the product's lifespan). Continuous monitoring will also include participant education, routine communication to ensure proper ATSB deployment and use, and the opportunity for household members to ask any questions or voice any concerns.

6.3.8 Entomological monitoring

6.3.8.1 *Monthly/quarterly mosquito catches*

Entomological data will be collected on a monthly basis from 10-12 households in each of 24 randomly selected study clusters (12 intervention and 12 control; total= 240-288 houses per month). Collection of monthly mosquito catches will use UV light traps. Human landing catches will be performed quarterly in 4 houses in each of 12 randomly selected clusters (6 control and 6 intervention clusters; total = 48 houses per quarter).

6.3.8.2 *Insecticide resistance monitoring*

Physiological and behavioural resistance to the ATSB toxin will be monitored annually by allowing adult mosquitoes reared from field-collected larvae or adult mosquitoes reared from the larvae of field-collected blood-fed or gravid adults to feed on the bait stations or according to other methods as they become available. As ATSBs employ an ingestion toxicant (in contrast to the contact insecticides used in LLINs and IRS), ATSBs have the potential to alter the physiological insecticide resistance profile in the mosquito population of insecticides used in LLINs and IRS. Thus, physiological resistance to insecticides used in IRS and LLINs will be assessed prospectively using WHO tube tests or CDC bottle bioassays. Additionally, a dinotefuran resistance assay is currently under development and may be used to monitor the development of resistance to dinotefuran during this trial.

6.3.9 Health-economic data

ATSB product and delivery costs will be collected following a standardized procedure to estimate the financial and economic costs of the intervention. Costs will be classified as capital or recurrent and traded vs non-traded. Capital costs will be annuitized and discounted using a 3% rate. These costs will be expressed in a common currency and year (2019 US dollars). Additionally, they will be converted into purchasing power parity adjusted International Dollars for internal comparison. Costs will be combined with efficacy measures from the trial to estimate incremental cost-effectiveness measures.

6.3.10 Collection of environmental parameters

Environmental parameters such as monthly rainfall and enhanced Vegetative Index (eVI) will be collected from online sites such as NASA's MODIS data repository.

6.3.11 Human safety monitoring

Systematic monitoring will assess safety by documenting the occurrence of any inadvertent exposures among the study participants to bait station contents (see 10.3, Safety monitoring and reporting, page 51).

7 METHOD: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

7.1 STUDY SITE

The study will be performed in Rarieda and Alego-Usonga sub-Counties of Siaya County, western Kenya. Malaria transmission is moderate to high and occurs year-round with peaks in June and July, and November and December following the long and short rains, respectively. Annual parasite prevalence from the continuous malaria indicator survey is estimated to be 36.5% by RDT among children under five years of age (unpublished data). In Siaya County, confirmed malaria incidence by passive case detection for 2016 was 585 per 1,000 population, and clinical (unconfirmed) malaria incidence rate was 261/1,000 (DHIS2 dashboard for Siaya County). The primary malaria vectors are *Anopheles funestus* and *An. arabiensis*. *An. gambiae s.s.* is a secondary vector. Malaria vector resistance to pyrethroid insecticides is documented in Kenya.

7.2 RECRUITMENT

Prior to the start of the study, we will hold community sensitization meetings with key leaders and stakeholders in the villages where the study will occur. Examples of key leaders and stakeholders include the county commissioner, chiefs and assistants, community advisory boards, village elders, community health volunteers, religious leaders, village reporters and youth. We will also hold "barazas" or community town halls. These meetings will serve to introduce the study and explain the purpose of the study, study components, who we might approach for enrolment and the general risks and benefits to the community at large. We will convene additional meetings with key leaders and stakeholders and hold additional barazas 2 to 4 times per year to provide a forum for questions and feedback.

When enrolment begins, study staff will approach prospective participants at their homes. Staff who will be approaching prospective participants will be trained to communicate clearly to participants that there is no requirement to participate, no pressure to participate, and no consequence for not participating.

If a prospective participant is undecided about enrollment on the day that study staff approach them, staff will be trained to leave the participant information sheet with the prospective participant and re-approach them within 1 to 3 days. At that time, if the prospective participant remains undecided, staff will explain to the prospective participant that if they want to enrol in the study at any later time, they can call the phone number provided on the participant information sheet.

7.3 ELIGIBILITY CRITERIA

The trial population as a whole consists of all *de facto* and *de jure* residents present in intervention and control clusters (and associated buffer areas) during the study period. The village boundaries, household and population in the study area in Siaya County were mapped and enumerated under an approved protocol (KEMRI SSC# 1801; CDC IRB# 3308) "Household socioeconomic status and health facility surveillance for infectious diseases in western Kenya" (HDSS). For the baseline assessment, 100 clusters were mapped. Eventually, 80 out of 100 baseline clusters will be selected for inclusion in the main trial using restricted randomisation to minimize imbalances in baseline predictors of the primary outcome (section 8.1, Allocation and randomization, page 32).

The eligible populations for each evaluation are described in detail in the following sections.

7.3.1 Eligibility criteria for clusters

7.3.1.1 *Inclusion criteria clusters*

- A grouping of contiguous rural villages in Alego-Usonga and Rarieda sub-counties of Siaya County
- A minimum of 200 households

7.3.1.2 *Exclusion criteria clusters*

- Hard to reach in the rainy season
- Refusal to participate by village elders

7.3.2 Eligibility criteria for participants in the cohort study

7.3.2.1 *Inclusion criteria cohort*

- A resident of a household within the core area of a study cluster, defined as living in the household in the recent four months and planning to live in the same household for the next 6.5 months
- Aged ≥ 1 year and < 15 years at the time of enrollment
- Written informed consent and/or assent

7.3.2.2 *Exclusion criteria cohort*

- A confirmed or suspected pregnancy. Pregnant women are excluded because they are eligible for intermittent preventive treatment of malaria in pregnancy (IPTp).
- Taking daily cotrimoxazole prophylaxis (because this has antimalarial effects)
- Known sickle cell disease (because they received antimalarial prophylaxis)
- Contraindication to artemether-lumefantrine, the medication used for parasite clearance

7.3.3 Eligibility criteria for households for ATSB deployment

7.3.3.1 *Inclusion criteria*

- Households located within one of the 40 clusters (core or buffer area) randomly allocated to the trial intervention arm with a least one permanent resident

7.3.3.2 *Exclusion criteria*

- Refusal of consent by the head-of-household to deploy ATSB on the outer walls (intervention villages only)
- Vacated compounds

7.3.4 Eligibility criteria for households for entomological monitoring

7.3.4.1 *Inclusion criteria households for entomological monitoring*

1. Household located within the core area of the cluster
2. Head of household or his/her representative is at least 18 years of age
3. Written informed consent for the collection of entomological data by the head of household or representative

7.3.4.2 *Exclusion criteria households for entomological monitoring*

- No residents sleeping in the household during the planned night of monitoring

7.3.5 Eligibility criteria for human landing catches

7.3.5.1 *Inclusion criteria human landing catches*

- Men aged 18 to 49 years
- Willingness and ability to work late at night for up to 7 hours at a time
- Willingness to take and tolerate a treatment regimen of the appropriate Kenya Ministry of Health (MoH) recommended antimalarial and chemoprophylaxis with 250 mg of mefloquine weekly to prevent malaria starting two weeks before the start of and until four weeks after completing HLCs
- Written informed consent

7.3.5.2 *Exclusion criteria human landing catches*

- Refusal/inability to work late at night for up to 7 hours at a time
- Unwillingness to take or intolerance/allergy to appropriate MoH treatment regimen or chemoprophylaxis

7.3.6 Eligibility criteria for participants in rapid ethnographic methods evaluation (community members)

7.3.6.1 *Inclusion criteria ethnographic evaluation (community)*

- A resident of a household within an intervention area defined as an ATSB area during the main trial or an ASB area during any preliminary studies
- Resides in a household at the time of ASB/ATSB deployment, where the ASB/ATSB was installed for at least one month.
- 18 years of age or older if participating in focus group discussions; 15 years of age or older if participating in in-depth interviews

7.3.6.2 *Exclusion criteria ethnographic evaluation (community)*

- Unable to provide consent

7.3.7 Eligibility criteria for participants in rapid ethnographic methods evaluation (ATSB monitoring assistants)

7.3.7.1 *Inclusion criteria ethnographic evaluation (ATSB monitoring assistants)*

- Serving as an ATSB monitoring assistant with experience installing ATSBs and monitoring the deployment
- Eighteen years of age or older

7.3.7.2 *Exclusion criteria ethnographic evaluation (ATSB monitoring assistants)*

- Less than one month experience (i.e. is new to the job)
- Unable to provide consent

7.4 WITHDRAWAL/FOLLOW-UP

Based on prior cohort studies in the area, we anticipate an approximate 20% refusal, LTFU, or withdrawal from each cohort. This is accounted for in the sample size calculations. The level of non-participation in household surveys is expected to be less than 20%.

7.5 BASELINE CHARACTERISTICS

The study anticipates summarizing a number of baseline characteristics at the individual, household and cluster level (Table 2).

Table 2: Baseline summary measures

Characteristic	Cohort	Continuous household survey
Cluster level		
Number of clusters	N	N
Cluster Size	Mean N HH (TOTAL HH)	Mean N HH (TOTAL HH)
Cluster Size	Mean N residents (TOTAL N)	Mean N residents (Total N)
Cluster Size (sampling areas)	Mean N residents (TOTAL N)	Mean N residents (Total N)
Cluster Size (buffer zones)	Mean N residents (TOTAL N)	Mean N residents (Total N)
Baseline Incidence	Mean incidence rate of clinical malaria in the baseline cohort per person-month (variance)	Mean incidence rate of clinical malaria in the baseline cohort per person-month (variance)
Baseline Prevalence		Proportion positive by RDT for *P. falciparum* at baseline
Household-level		
HH size	Mean N residents (SD)	Mean N residents (SD)
LLIN ownership (at least one LLIN per household)	Proportion HH with >=1 LLIN (First interview)	Proportion HH with >=1 LLIN
LLIN ownership (at least one LLIN per two people in the household)	Proportion HH with >=1 LLIN per 2 residents (First interview)	Proportion HH with >=1 LLIN per 2 residents
Individual-level		
Age	Mean age (SD)	Proportion under five
Sex	Proportion of female	Proportion of female
HH size	Mean hh size of participant's HH (SD)	Mean hh size of included hh (SD)
Net Use	Proportion Slept under the net night before the survey	Proportion (tested population) slept under the net night before the survey

7.6 INTERVENTION (ATSBS)

7.6.1 ATSB

7.6.1.1 *Deployment of ATSB in the study area*

We will use ATSBs from Westham Co. (Israel) containing Dinotefuran, a neonicotinoid insecticide effective at rapidly killing mosquitoes (See Section 11.3, Risks and Benefits, page 55 for safety information).

ATSBs will be installed on all structures of consenting households in intervention areas that meet the following criteria:

- Complete roof with eaves
- At least three complete walls
- Wall length exceeds one meter
- Wall height exceeds 1.8 meters

ATSBs will be affixed to each structure according to the instructions from the manufacturer as follows:

- Height of 1.8 meters or as high as possible above ground and out of the reach of children and animals
- Exterior walls of structures
- Wooden rods inserted on the top and bottom of the bait station to keep the station flat
- A string tied to the wooden rods to hang the bait station on two nails nailed into the household structure walls.
- ATSB membrane facing outwards and protected by eave

The number of ATSBs (two or three) to be installed per structure will be determined during a field trial conducted from May 2021 to August 2021 (SSC Protocol 3613; CDC IRB # 7112; LSTM REC # 18.015). A cadre of monitoring assistants will be recruited from participating communities. The monitoring assistants will receive training on how to unpack and correctly install the bait stations. The monitoring assistants will be responsible for providing individual-level household orientation for the ATSB. This orientation will include the following instructions:

Figure 5 ATSB station in Mali

- Do not remove the bait station for any reason
- Replace the bait station promptly should it fall down (provided it does not appear to have been damaged)
- Keep bait stations that may be temporarily uninstalled (e.g. awaiting assistance in reinstallation) out of reach from children and animals
- Contact the monitoring assistant if the bait station becomes damaged or goes missing
- Do not dispose of the bait stations. If, at any time, the household wishes to uninstall the stations, a monitoring assistant should be contacted for removal and proper disposal.

When monitoring assistants visit households for bait station installation, they will provide an information sheet and seek informed consent (see ATSB Participant Information and Informed Consent Forms). ATSBs will be installed only at households where the head of the household or his/her representative provides informed consent. Household members will have the opportunity to ask questions and voice any concerns.

Bait stations will be marked with a unique identifier. At the time of installation, the identifiers of ATSBs for a given household will be entered into a questionnaire allowing a linkage with data collected from that household. Data collection will include a household ID, household head name and contact information, as well as household GPS coordinates.

7.6.1.2 *Community sensitization*

Prior to ATSB deployment, community sensitization activities will be conducted to prepare communities for intervention and research activities. Community sensitization begins with the County and sub-County Health Management teams and the Division of National Malaria Program.

Community sensitization activities will be informed by initial qualitative research activities undertaken to understand community member knowledge and perceptions regarding ATSBs based

on experiences from the validation studies. Community sensitization meetings (which may include 'barazas') will be held in all intervention area communities. All community members will be invited to the meetings, and monitoring assistants and study staff, together with community leaders (e.g. elders, school teachers, religious leaders), will provide an overview of the ATSBs and instructions, as noted above. The community leaders and monitoring assistants, study staff, and community leaders will be trained about the ATSBs and will answer community member questions and address concerns. If they are unable to address specific questions or concerns, the monitoring assistants will refer these questions to the field coordinator. Where appropriate, local media may be used to disseminate messages to sensitize the community to the intervention and the research. This may include posters, pamphlets, or other printed materials. At each ATSB monitoring visit, and at the time of ATSB removal and replacement, household members will have the opportunity to ask questions and voice concerns to the ATSB monitors who will respond, capture this information, and report any questions that they are unable to respond to to the field supervisor who will then work to respond to the household.

Sensitization meetings will also be held in control clusters to explain the trial and encourage appropriate care-seeking behaviour and usage of malaria prevention methods, including LLINs.

7.6.1.3 *Monitoring of ATSBs*

At the first visit during month 0, new ATSBs will be installed. At month 7, month 13, and month 19 (every six months), all installed ATSBs will be replaced with new ATSBs. Full coverage of fully functional ATSBs will be maintained for the duration of the study. Community-based monitoring assistants will be trained and will be responsible for visiting intervention households monthly throughout the trial. Additionally, household heads in intervention areas will be instructed to contact monitoring assistants for a replacement bait station if one is damaged or missing in between monitoring visits.

The monitoring assistants will be equipped with a supply of ATSBs and necessary materials for installing, replacing or re-hanging damaged or missing devices. During each monthly visit, the monitoring assistants will ensure eligible structures in study areas are covered with correctly installed ATSBs according to the manufacturer instructions. They will replace damaged or missing ATSBs as needed and record information about the ATSB condition in electronic data capture forms on a smartphone or tablet. The monitoring assistants will attempt to recover any missing ATSBs for proper disposal. They will respond to and record questions or concerns voiced by the household members to the field supervisor. At the end of their sixth month period, or if they are damaged or missing, they will be collected and incinerated in a high-temperature incinerator, per manufacturers instruction (see Section 16.3, Annex III: ATSB Stations: Disposal options assessment, page 80).

7.6.2 Control cluster interventions

Between March and June 2021, the Government of Kenya is planning a mass LLIN distribution campaign throughout Siaya County (the study area is within Siaya County). Through our baseline continuous household survey (cMIS), we will evaluate LLIN coverage in all intervention and control clusters. Based on the findings, we may plan a "top-up" distribution to ensure equal coverage across arms.

7.6.3 Other malaria control interventions

Community-case management of malaria by community health volunteers is an active intervention promoted by the Ministry of Health in this area. In this strategy, community health volunteers test and treat participants encountered in the households who complain of symptoms compatible with

malaria. Additionally, in September 2019, the Kenya Ministry of Health began a phased implementation of GSK's Mosquirix vaccine in children aged 5-17 months of age. Rarieda sub-county was chosen as an initial vaccinating sub-County, whereas Alego-Usonga was not. To control for the impact of RTS,S/AS01 on our study outcomes, we will ensure a balance of clusters between arms in Rarieda and Alego-Usonga sub-Counties. Additionally, we will record the vaccination status of all children <5 years of age from the maternal-child booklet or from vaccination cards. Where available, we will take a photograph of the child's vaccination records. Where not available, we will use maternal recall. The Kenya Division of National Malaria Program (DNMP) does not currently have plans to perform IRS in Siaya County during the trial period. Should IRS be implemented in the trial area during the trial, the study team will monitor timing and coverage of the campaign at a household and cluster level but will not be responsible for regulating or "topping up" IRS should DNMP initiate spraying in the area.

7.7 ADHERENCE AND PROTOCOL DEVIATIONS

Both individual and cluster level adherence measures will be defined and pre-categorized prior to final analysis and used to categorize the per-protocol trial population. Since the intervention is deployed on a group basis rather than individually, adherence definitions will take account of this.

7.7.1 Cluster-level adherence

In intervention clusters, adherence at the cluster level will be defined as a cluster where ATSBs were deployed and replaced according to the planned schedule. Non-adherence in intervention clusters will be defined as clusters where there was more than one-month delay in ATSB deployment during a two year period.

7.7.2 Household-level adherence

Household-level adherence will be evaluated in the intervention cluster arms through ATSB monitoring visits. For each household, "expected ATSB-time" will be calculated by multiplying the total number of expected ATSBs hanging (2-3 ATSBs per structure) by the duration of time between visits (approximately four weeks). "Actual ATSB-time" will be calculated by multiplying the observed number of ATSBs during the monitoring visit by the duration of time they were hanging. The ratio of "actual ATSB-time" over "expected ATSB-time" will be expressed as a percentage and used as the measure to evaluate household-level adherence. For example, if a household has ten structures, and the intention is to have two ATSBs per structure, there should be 80 ATSB-weeks over four weeks (10x2x4). If the household had only one ATSB hanging on each structure between visits, the household would have an observed ATSB-time of 40 ATSB-weeks (10x1x4) and a household adherence of 50% (40/80).

7.7.3 Individual-level adherence to antimalarial treatment among cohort members

A random subset of cohort participants who have recently been treated for malaria may be re-visited within one week to assess adherence to the study medication. At this time, study staff will ask questions about the total number of doses taken and request to view the blister pack that contained the treatments that the participant took.

7.7.4 Protocol deviations

Protocol deviations will be considered as the cluster and individual level using the above-described definitions for adherence. Protocol deviations related to failure to carry out other study procedures such as outcome assessment on a standardized schedule will not be considered reportable to DSMB unless they affect an entire cluster and delay primary outcome assessment by more than two

months. Protocol deviations related to failure to deliver or replace ATSB will be summarized in the final trial reports and incorporated into the calculation of adherence.

7.8 SAMPLE SIZE

The number of study clusters identified for this study was driven by sample size considerations for the primary endpoint, malaria case incidence.

7.8.1 Malaria case incidence cohort

7.8.1.1 *Main trial*

The sample size was calculated using the 'Tests for the Difference Between Two Poisson Rates in a Cluster Randomized Design' module in PASS 2020 (©NCSS, Kaysville, Utah). The observed event rate in this age group was 1,128 per 1000 person-years in the control arm of a recently completed mass test-and-treat trial in this area. A more conservative event rate of 845/1000 will be used, which is 25% lower than the previously observed event rate of 1,128/1000 person-years. This is done to account for an estimated 7.4% overall reduction in event rates in children 1-<15 years due to the implementation of the RTS,S/AS01$_E$ vaccine (vaccine efficacy 39.0%) in two-third of the study area in children 1-<5 years of age (28.6% of the sample study cohort) (0.39x0.67x0.286=0.074), plus a further 17.6% reduction in malaria due to unforeseen changes in environmental factors, or boosting of other malaria control measures such as the scaling up of integrated community-based case management. The coefficient of variation in this previous study was 0.4.

A total sample size of 2,240 person-years (1,120 per arm, or 28 person-years per cluster) is required to detect a ≥30% reduction in the incidence of clinical malaria among children aged 1-<15 years (the primary outcome) from 845 per 1000 person-years in the control arm to 592 in the intervention arm over two years, allowing for 20% loss of person-time due to LTFU, or exclusion of person time after a clinical event treated with artemether-lumefantrine during a six month follow-up period resulting in 1,760 person-years completed (22 person-years per cluster, 880 person-years per arm) (80 clusters [40 per arm], CV=0.4 in both arms, two-sided alpha=0.049, power=90%). No sample size inflation is required two allow for two interim analyses because a similar sample size is needed (2,240) for a study with a final two-sided alpha of 0.049 as for a study with a single analysis using a two-sided alpha of 0.05.

The intention is to follow each child for 6.5 months. This includes two weeks of lead-in time that do not contribute to the analysis. These are the first two weeks after the initial presumptive treatment with artemether-lumefantrine to clear any existing parasitaemia. This will then be followed by six months of follow-up time that contribute to the analysis. We will use a more conservative average follow-up time of five months per participant to allow staggered enrolment of participants over time. This means that not all children towards the end of the 2-year trial will complete the full 6.5 months. The 2,240 person-years will thus be obtained by sampling approximately 67.2 individuals for an average of five months each in 80 clusters (67.2x[5/12]x80=2,240).

The same sample size will also have 80% power to detect a 26% reduction from 845 to 622 per 1000 person-years with all other parameters kept the same, or 80% power to detect a 30% reduction if the CV was 0.488 instead of 0.4. Similarly, the study would have at least 80.0% power to detect a significant difference at the first interim analysis when 50% of the events have occurred in the control arm if the effect size is 41.2% instead of 30% (alpha=0.001, using Haybittle-Peto type boundaries, see 9.4.1, Interim analysis, page 44).

7.8.1.2 *Baseline cohort*

The baseline cohort will be conducted during a period of approximately six months in 100 (instead of 80) potential clusters before the deployment of ATSB. The sample size for the baseline cohort will be 550 per year, obtained by following 11 participants per cluster for an average of five months each (11x[5/12]x100). The sample size is based on similar sample size considerations per cluster as for the main trial but adjusted to a six month instead of a 2-year period. The average of five months each (with a maximum follow-up time of 6.5 months per participant) is used to take a staggered enrolment into the cohort into account (i.e., not all participants will have contributed the full 6.5 months before the start of the main trial).

7.8.2 Continuous malaria indicator survey to assess malaria parasite prevalence

7.8.2.1.1 Main trial

The continuous malaria indicator survey (cMIS), conducted under a separate protocol, provides adequate power to detect a 30% reduction in the all-age malaria prevalence detected by RDTs per year from 29.0% to 20.3%. The 29% prevalence is based on the observed all-age prevalence in Rarieda sub-county (29%) (representing two-thirds of the study area) and in Alego-Usonga (47.3%), representing one-third of the study area. The 47.3% in Alego-Usonga is based on cMIS data in neighbouring Karemo. The prevalence estimate in Rarieda is reduced from 29% to 27.7% to account for a 50% drop in malaria prevalence in children < 5years of age who will receive the RTS's vaccine. Because this age group only represents 13.9% of the population, the anticipated impact of RTS,S on the all-age prevalence in Rarieda is modest. The pooled estimate of the RTS's adjusted all-age prevalence of 27.7% in Rarieda and 47.3% in Aleg-Usonga is 34.1%. We propose to use a more conservative prevalence of 29% to allow a 15% reduction in malaria prevalence due to annual variations in environmental conditions (e.g. rainfall, temperature) (0.85 x34.1%=29%). This requires 3,520 participants per year (44 per cluster, including 9 non-responders and 35 responders) (ICC=0.05, power=90%, two-sided alpha=0.05, and assuming 20% non-responders, e.g. refusals, not at home, etc.). The values for the intra-cluster correlation (ICC), parasite prevalence, and non-response rates were estimated from the ongoing cMIS study. Where possible, households that are included in the first year will be excluded in the second year. Over 2-years, and assuming no overlap in participants between the first and second year, a sample size of 88 per clusters (including 18 non-responders and 70 responders) would provide 80% power to detect a 23.7% reduction or 90% to detect a 27.3% reduction (ICC=0.05, alpha=0.05). Similarly, 70 responders per cluster after two years would provide 80% power to detect a 30% reduction if the ICC is 0.091 instead of 0.05, or 90% power if the ICC is 0.064.

7.8.2.2 *Baseline*

A similar annual sample size of 44 per cluster, including 9 non-responders and 35 responders, will be used in 100 clusters during the baseline year before the deployment of ATSBs in the intervention arms.

7.8.3 Entomological monitoring

Twelve intervention clusters and 12 control clusters will be selected for entomological monitoring. Based on previous field research in Mali, large reductions in mosquito density are anticipated, up to 90% (although density reductions may be dependent on the season due to seasonal fluctuations in abundance). A minimum reduction in density of 50% was used for sample size calculation.

Ten 10 entomological collections per cluster per month are required to detect a 50% reduction in mosquito densities per CDC UV light trap (two-sided alpha=0.05, power=80%, ICC=0.38, 24 clusters

[12 per arm]). For the impact of ATSBs on parity or sporozoite rates, all unfed mosquitoes captured alive will be used to estimate parity rates. All Anopheles mosquitoes collected during the study will be subjected to ELISA to estimate sporozoite infection rates.

7.8.4 Rapid ethnographic methods

Focus group discussions (FGD) and in-depth interview (IDI) will be implemented at three discrete time periods: 1) before ATSB deployment, 2) at least one month after the first round of ATSB deployment, and 3) at least one month after a subsequent ATSB deployment. Each FGD will involve six to eight participants. FGDs will be segregated by sex and community members versus monitoring assistants. In the pre-ATSB deployment stage a total of six FGDs will be conducted; four among community members and two among monitoring assistants. In each of the post-ATSB deployment rounds, twelve FGDs will be conducted among community members and two among monitoring assistants. IDIs will be conducted among community residents. A total of eight will be conducted in the pre-ATSB deployment period, and then twelve each during the post-deployment rounds.

8 METHODS: ASSIGNMENT OF INTERVENTIONS

8.1 ALLOCATION AND RANDOMIZATION

Restricted randomization will be used to allocate 80 of the 100 baseline clusters to intervention and control arms for the main trial to minimize any imbalance between study arms on key baseline characteristics. The steps to achieve restricted randomization will be conducted by a study team member who is not responsible for trial implementation. The steps are as follows:

1. Establish balance criteria. The factors described in the table below may be considered for suitability as restriction criteria.
2. Generate a list of at least 100,000 randomizations
3. Check randomizations against balance criteria and drop those that do not fit
4. Assess the number of randomizations left. There may be a need to relax criteria and start again if fewer than 10,000 acceptable randomizations remain.
5. Test remaining set of potential randomizations for validity, specifically that all clusters are being independently assigned to study arms (e.g. check that no two clusters are always jointly assigned to the same arm).
6. Randomly choose a randomisation.
7. Flip a coin to determine if arm A or arm B is ATSB or control.
8. Step 6 and 7 to be done in public with community participation.

Table 3: Factors to consider for restricted randomisation

Covariable/ endpoint	Restriction criteria	Data source	Analytic method
Malaria disease incidence	The difference in mean clinical case incidence between trial arms (size of difference to be assessed when data are available)	Baseline cohort	The difference in disease incidence of cluster summaries between study arms
Bednet use	The difference in mean proportion of persons slept under any net night before survey between trial arms ≤5 percentage points	Baseline survey	The difference in means of cluster summaries of the proportion of persons of all ages slept under any net night before survey between arms

Population	The total population size of the larger trial arm is no more than 10% larger than the smaller arm	Enumeration datasets	Sum(pop size of clusters Arm large)/Sum(Pop size of clusters arm Small) less than 1.10
RTS,S/AS01 vaccinating area	Number of clusters in intervention and control arm balanced by vaccinating or non-vaccinating areas for RTS,S/AS01	Kenya National Vaccinations and Immunizations Programme (NVIP)	N in Arm A== N in Arm B
Housing density*	The difference in mean housing density between trial arms ≤ 0.3 SD of overall cluster level housing density	Enumeration + cluster boundaries GIS files Or Remotely sensed data (GRUMP/WorldPop) plus Cluster boundaries GIS	SD(cluster estimates of housing densities)*0.3 ≥ |mean(cluster estimates housing density Arm a) – mean(Cluster estimates of housing density Arm b)|
HF location	Number of clusters with a primary care facility exactly balanced across arms	Study team documentation	N in arm A == N of Arm B
Altitude	Differences in mean altitude of cluster centroids between trial arms ≤ 0.3 SD of overall cluster level mean altitude	Digital Elevation Model (ASTER) combined with (GIS) shapefiles for cluster boundaries.	SD(cluster estimates of altitude)*0.3 ≥ |mean(cluster estimates of altitude Arm a) – mean(Cluster estimates of altitude Arm b)|
Entomological data collection	The number of clusters with entomological data collection planned is exactly equal across study arms	Study team self-report	N in arm A == N in arm B

*Either urbanization or housing density will be selected; these variables are likely collinear.

8.2 BLINDING

Allocation of study arms will not be blinded to the participants, the deliverers of the intervention, or the main investigators. Sham ATSBs will not be deployed in control areas because it is logistically not feasible to produce the number of ATSB stations needed for both intervention and control arm. The potential for bias among operator-dependent mosquito catches (indoor and outdoor aspirations) will be minimized using a standardized protocol. Additionally, the potential for bias in mosquito catches using CDC light traps is very low. The potential for changes in human behaviour affecting malaria control intervention coverage, namely LLIN use, will be minimized through comprehensive community engagement and communications. LLIN use will be promoted in intervention and control areas. Additionally, study teams will monitor LLIN use in intervention and control areas to document changes throughout the life of the study. Laboratory processing of mosquito and human blood specimens will be blinded.

To further minimize bias, we will use an objective primary outcome measure and mask all laboratory staff to the treatment assignment of individual participants. The trial statistician will also be blinded regarding the allocation arm when the statistical analysis plan is developed and the analytical syntax is written, which will be validated and completed using dummy randomization codes. The actual

allocation will only be provided to the study team after locking the database and approval of the statistical analysis plan by the independent DSMB before they review any trial results.

9 METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

9.1 DATA COLLECTION

Outcomes are assessed using different sub-studies, including cohort studies, continuous household surveys, passive clinic- and CHV-based surveillance and ethnographic and economic studies; for an overview, see Section 5, Objectives and outcomes, page 15. The details of each of these components are outlined below.

9.1.1 COVID-19 mitigation efforts

As a result of the COVID-19 pandemic, the Government of Kenya and the KEMRI SERU have developed guidelines to be followed within research trials to protect participants and study staff from SARS-CoV-2 transmissions (KEMRI-SERU section 3.2.5, Ref: KEMRI/SERU/REC/GUIDE/001 of 22nd June 2020). These mitigation efforts are periodically updated by the Ministry of Health and KEMRI. We will adhere to the prevailing Ministry of Health and KEMRI guidelines at the time that the study commences and will adopt any new recommendations during the course of the trial.

9.1.2 Cohort study to assess the incidence of clinical malaria

Households with participants aged 1 to <15 years of age will be randomly chosen from the household in the census database. A single resident aged 1 to <15 years will be selected from these households to be enrolled in the cohort. They will be followed for up to 6.5 months, including two weeks of lead-in time for parasite clearance and six months of subsequent follow-up, contributing to the analysis person time). The sampling frame of households may be updated based on findings from subsequent routine CHV censuses in the study area. A baseline cohort study will be conducted before the deployment of ATSB to inform the restricted randomisation, followed by a cohort study, to assess the impact of ATSB. The procedures in these cohorts will be similar, as outlined below.

9.1.2.1 *At recruitment/enrolment*

- Informed consent will be administered to the parent/caregiver, and assent to the participant if he/she is 13-<15 years of age
- A fingerprick blood sample (~250µL or 1mL) will be collected to perform an RDT and to prepare approximately five dried blood spots (DBS) on filter paper for subsequent molecular and potentially serological testing and for evaluation of mosquito salivary antigens
- All cohort members will be treated with artemether-lumefantrine (AL; first-line antimalarial in Kenya) irrespective of their RDT result to clear any subpatent infections that may exist
- A questionnaire will be administered to the head of the household to assess household assets for the construction of socio-economic status (SES) categories and to assess household malaria control measures (e.g. number of LLINs, housing construction)
- A questionnaire will be administered to the parent/caregiver and/or the participant to assess activities of interest, including medical and vaccination history, medication use, inclusion in other clinical trials, care-seeking behaviour, LLIN use, daily commuting and travel information, and information about the structure that the participant sleeps in
    - A photograph will be taken of vaccination history and pertinent medical records from the maternal child health booklet or other records

    - For participants enrolled in the HDSS or clinical studies, we will link the cohort data to their study/HDSS records
- For young women of childbearing age (12-14 years), pregnancy status will be evaluated in a private and confidential location through the following algorithm:
    - If the woman has had menarche, her last menstrual period was >=6 weeks ago, and if she has any suspicion that she may be pregnant, then she will be offered a urine pregnancy test
    - If she declines or is found to be pregnant, she will be considered ineligible for the cohort
- A photograph may be taken of the participant to create a study identification badge that the participant will keep for identification by study staff for scheduled and sick visits

9.1.2.2 *Parasite clearance confirmation visit (2 weeks after enrolment)*

- Before this visit, the study team will call the cohort member to remind them of the upcoming visit and reschedule if necessary. Up to three visit attempts will be made to complete the parasite clearance confirmation visit.
- Two weeks after the enrolment visit, the household will be visited and a finger-prick blood sample (~250µL to 1mL) will be drawn to prepare five dried blood spots, and to prepare a blood smear for parasite clearance confirmation.
- If the participant is febrile at this visit, the staff member will review the RDT result from the enrolment visit.
    - If the enrolment visit RDT was negative, the participant will be re-tested with an RDT and if positive, the participant will be ineligible for the cohort and second-line antimalarial treatment will be administered as per national guidelines (e.g. dihydroartemisinin-piperaquine). If the RDT administered during this visit is negative, we will proceed with the blood smear.
    - If the enrolment visit RDT was positive, the blood smear will be expedited.
- If the participant is found to be positive for malaria by microscopy, we will consider the participant ineligible for the cohort and will withdraw him/her. A staff member will return to the house to convey this information and provide second-line antimalarial treatment as per national guidelines (e.g. dihydroartemisinin-piperaquine).

9.1.2.3 *At each monthly cohort visit (starting 4 weeks after enrolment)*

- Prior to each follow-up visit, the cohort study team will call cohort members to remind them of the next visit and reschedule, if necessary, to minimize loss to follow-up. Up to three visits will be made to each cohort study household to complete a follow-up visit.
- At each of these visits, a finger finger-prick blood sample (~250µL to 1mL) will be drawn to prepare approximately five dried blood spots for testing, as indicated in the enrolment visit.
- If the participant has an axillary temperature of ≥37.5^{o} C or reported history of fever in the last 48 hours, a malaria RDT will be performed using blood from the same fingerprick. Those who test positive for malaria by RDT will be treated at the household according to the Kenya Ministry of Health Guidelines unless they already received appropriate antimalarial treatment from other sources in the previous seven days. Cohort members who do not have objective fevers or report a history of fever in the last 48 hours will not be tested for malaria by RDT.
- For women of childbearing age, pregnancy status will be evaluated as described in the enrolment visit section. Those in whom a pregnancy test is indicated but who decline and those who have a positive pregnancy test will be withdrawn from the cohort. These women

may opt to be visited and evaluated for malaria, free of charge for the duration that they would have been in the cohort.

- A questionnaire will be administered on a tablet or smartphone to the participant or his/her parent/guardian, including questions about the history of recent illness (including AEs and SAEs), care-seeking, LLIN use, and travel and commuting history. If the cohort member sought care between scheduled visits, we will copy any relevant information from these health records to evaluate any malaria diagnostics performed and antimalarial treatment given
- A follow-up visit in four weeks time may be scheduled at this time. Parents/guardians and the participant will be reminded to call the study staff at the number provided on the consent form if the participant becomes ill before the next scheduled visit.
- The limited care provided by the study team includes any care related to study procedures, malaria illness, or other uncomplicated acute illnesses such as acute respiratory or gastrointestinal disease. The study will not be responsible for the care of pre-existing conditions or chronic or traumatic conditions diagnosed during the trial.

9.1.2.4 *Sick visits (participant initiated visits occurring between scheduled monthly visits)*

- Study staff will tend to cohort participants for sick visits as described above
- During these sick visits, study staff will administer a "sick visit" questionnaire including questions about current illness and any associated care-seeking behaviour or medications ingested.
- Questions about physical interaction with or ingestion of ATSBs will also be included for AE and SAE monitoring.
- Will collect a finger- or heal-prick to collect 250 µL to 1 mL of blood to prepare approximately five dried blood spots on filter paper and for any other diagnostic tests that are clinically indicated based on the participant's presentation
- In the setting of identifying that a cohort member sought care from outside of the study (identified either from a phone call or subsequent scheduled visit), study staff will attempt to gather records from the facility, CHV or pharmacy where the cohort member sought care

PCR and serological testing of the DBS specimens collected during the study will not be used for care.

9.1.3 Continuous household survey

9.1.3.1 *Continuous malaria indicator survey (cMIS)*

Community malaria infection prevalence will be evaluated through an ongoing protocol involving participants of all ages, "Malaria Indicator Household Surveys to evaluate the impact of malaria transmission reduction activities in Siaya County, western Kenya: a continuous rotating panel survey"; short title, "Continuous Malaria Indicator Survey (cMIS)" [KEMRI SERU Protocol# 2773; CDC IRB# 6733; LSTM REC# 14.009; PATH RDC# 0777]. The survey will include malaria blood testing by RDT and PCR. The RDT result will dictate malaria treatment in the field, and PCR results will be processed at a later date to estimate the secondary outcome of infection prevalence by PCR. The individual and household questionnaires will capture information about malaria intervention coverage (e.g. LLIN ownership and use), housing characteristics, and household demographic information. The surveys will also measure a set of indicators regarding ATSB knowledge and perceptions.

9.1.3.2 *Brief description of cMIS procedures*

- Households are randomly selected for household visits

- Staff members administer informed consent
- Staff members administer the cMIS questionnaire on a password protected study tablet, which includes questions about the history of illness, care-seeking, malaria prevention methods and coverage
- Study staff collect blood (250 µL to 1 mL) from a finger- or heal-prick to prepare approximately five blood spots on filter paper and to perform a rapid diagnostic test. If the RDT is positive, the study staff member treats the participant per Kenya Ministry of Health guidelines

9.1.4 Passive case detection

Confirmed malaria case incidence data will be collected from outpatient health facilities, ANC clinics, and from CHVs providing diagnostic testing in the community through the Kenya Ministry of Health. These are routine surveillance data collected by the Ministry of Health and do not include personally identifiable information. Numbers of participants with suspected malaria, tested for malaria (RDT or microscopy), diagnosed with malaria and treated for malaria are recorded in the routine registries collected at these facilities and by CHVs.

The population denominator for incidence calculations will be derived from the house-to-house enumeration and census.

9.1.5 Entomological monitoring

Entomological monitoring activities will include routine indoor and outdoor mosquito collections using CDC UV light traps and human landing catches (HLC), monitoring for insecticide resistance, and ATSB durability.

9.1.5.1 *UV light traps*

1. Twelve intervention area and 12 control area clusters will be randomly selected for entomological monitoring using UV Light traps.
2. Entomological field assistants will receive training in the study methods and procedures for mosquito collections.
3. Informed consent will be administered to the head of household
4. UV light trap collections will be conducted monthly for the duration of the trial. The household sampling frame generated during the census will be used to select a random sample of 10-12 households per cluster.
5. Collections from clusters will be completed in pairs: one intervention and one control cluster pair. If feasible, collections from all 10-12 households in each of the 2 clusters will be completed in one night. If this is not feasible, collections will be completed over two nights from 5-6 households per cluster per night.
6. In each selected household, a UV light trap will be hung at the foot of a bed or sleeping space by the entomology field team between 1700-1800HRS in the evening. The UVLT should be set next to a bed or sleeping space with a net hanging over it. The house owners will be instructed not to touch it until removed by the team the next morning
7. An additional light trap will be set up outdoors
8. In the morning, the entomology field assistants will visit the household, ensure the UVLT is still running and then carefully remove the collection cup to ensure no mosquitoes escape. Mosquitoes will be returned to the KEMRI CGHR laboratory in Kisian or a field laboratory, where mosquitoes will be sorted and processed for further analyses.

9.1.5.2 *Human landing catches*

1. Six clusters not included in the monthly UVLT sampling will be randomly selected from each arm, and within each cluster, four households will be purposively selected for quarterly indoor and outdoor mosquito collections using human landing catches. Each household will participate in this collection for two nights.
2. Selected households will be visited in advance of the collection night and provided information about the study. Informed consent will be sought from the head of the household or his/her representative.
3. A team of 6 collectors will be consented per house. They will be divided into pairs, and each pair will work up to a 6-hour shift during the night. Collections will begin at 5 pm in the evening and continue through 11 am the following morning.
4. Collectors will work for 45 minutes each hour and then take a 15-minute break to rest, take food if necessary and prepare for the next hour of collection. Each pair of collectors will work for 6 hours before a new shift will take over.
5. Prior to the HLC, collectors will be trained to properly aspirate mosquitoes, ideally before they are bitten, and will have ample time during training to practice the technique so as to minimize bites during collections.
6. The collectors will sit in fixed spots, one inside the house and one outside at least 5m away from the house. They will then expose their lower legs, and using a torch (flashlight) and a mouth aspirator, they will collect mosquitoes that land on their lower legs. Collected mosquitoes will be placed in individually labelled paper cups with a separate cup for each hour of indoor collection and outdoor collections.
7. Mosquitoes will be returned to the KEMRI CGHR laboratory in Kisian or a field laboratory in the study area where mosquitoes will be sorted and processed for further analyses.
8. Collectors will be provided with mefloquine 250 mg weekly for prophylaxis, starting two weeks prior to the HLCs as per manufacturer guidelines. Research has shown that with proper prophylaxis, participants in human landing catch collections are at a reduced risk of malaria infection compared to non-participants living in the same community.[20] To further minimize risk to field workers, they will be instructed to wear long-sleeve shirts during the collections to prevent mosquitoes from landing and biting them on the arms (only the legs are exposed for the collections). Collectors will also be provided with free malaria testing and treatment if they become ill during the course of the HLCs and for up to 4 weeks after.

9.1.5.3 *Insecticide resistance monitoring*

1. Insecticide resistance monitoring will be examined at the end of years one and two and will include testing dinotefuran, permethrin, and either deltamethrin or alphacypermethrin.
2. *An. gambiae s.l.* mosquitoes will be collected as larvae while *An. funestus* will be collected as adults from inside houses. Fed/gravid *An. funestus* will be allowed to lay eggs. Immature mosquitoes collected as larvae or from adult *An. funestus* will be reared to the adult stage in the insectary at the KEMRI CGHR in Kisian.
3. Adults that are 2-5 days old will be exposed to the insecticides using standard WHO tube tests to permethrin, deltamethrin and alphacypermethrin [21].
4. Twenty to twenty-five mosquitoes per tube (or bottle) will be run, and enough tubes/bottles will be run to have a minimum of 100 mosquitoes exposed (the total number of mosquitoes will be dependent on the amount able to be collected).
5. WHO test papers for dinotefuran are not available. Resistance testing for this insecticide will be done using a topical application of a diagnostic concentration to the thorax of adult mosquitoes, and mortality will be recorded after 24 hours.

9.1.5.4 *Bait station durability*

1. To examine the durability of the bait stations during the first 6-month deployment, a selection of ATSBs will be randomly sampled from households within ATSB study clusters. Stations collected from households will be immediately replaced with new stations.
2. The bait station will be placed in a 30cm x 30cm x 30cm cage and 100 female *An. gambiae* or *An. arabiensis* (collected as larvae and reared in the lab) will be introduced into the cages after an appropriate period of starvation.
3. Mortality will be recorded at 24 hours.
4. The number of dead and live mosquitoes will be recorded at 48 hours.

9.1.5.5 *Entomological laboratory procedures*

1. Specimens will be processed to estimate species composition, density, age structure, sporozoite rate, and EIR estimation.
2. Mosquitoes will initially be identified morphologically using standard dichotomous keys
3. All female anopheline mosquitoes will be tested for the presence of *Plasmodium spp.* sporozoites using ELISA
4. Mosquitoes identified as *An. gambiae* s.l. will be identified to species using standard PCR. A subset of *An. funestus* will be identified to species by standard PCR methods.
5. A subset of live female mosquitoes collected by UVLT or HLC will be dissected and examined for dilatations in the ovarian duct as a proxy for age (each dilatation represents an egg batch laid).

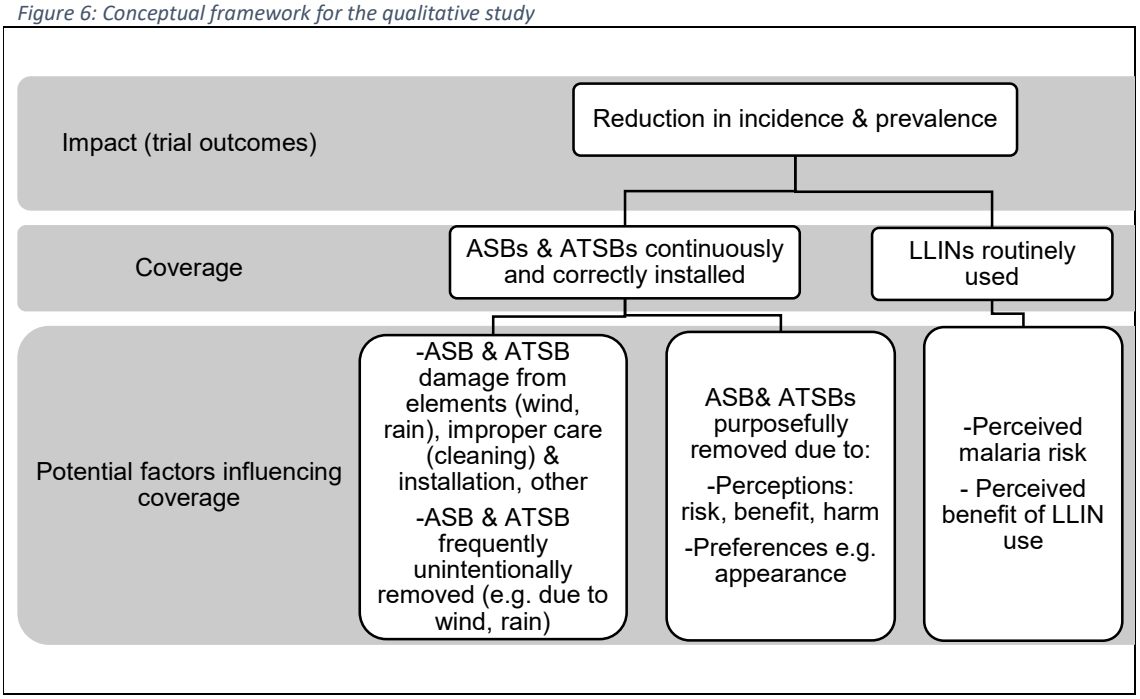
9.1.6 ATSB Intervention monitoring

1. ATSB monitoring assistants will be trained on proper installation, adjustment, and removal and transport of ATSBs on structure walls, administering an ATSB questionnaire, and responding to questions or concerns raised by household members.
2. After administering informed consent and ATSB installation community-based, ATSB monitors will visit households in intervention clusters on a monthly basis
3. ATSB monitors will complete a questionnaire programmed onto a tablet or electronic data capture form to assess the presence of each ATSB and/or whether it has incurred any damage
4. If an ATSB has been damaged, the monitor may photograph the damaged ATSB
5. Damaged or missing ATSBs will be replaced by ATSB monitors at each visit
6. ATSB monitors will instruct the head of the household to contact the study team if an ATSB is damaged or is missing between each visit so that the ATSB monitor can return to replace it to ensure high ATSB coverage rates
7. ATSB monitors will additionally respond to any questions or concerns that household members have about the ATSB or the trial. They will refer questions they are unable to answer to the field supervisor for further consideration and response.

9.1.7 Rapid ethnographic methods

The qualitative component of this study is designed to understand potential factors that influence coverage, including 1) ASB and ATSB coverage, defined as the continuous and correct installation of the ATSBs, and 2) LLIN coverage, defined as routine use by household members each night (see Figure 6: Conceptual framework for the qualitative study, below).

Figure 6: Conceptual framework for the qualitative study



A series of three qualitative evaluations will be conducted as part of this trial: 1) after an entomological validation trial with ASBs, but before the main trial, 2) during the first year of the ATSB main trial, and 3) during the second year of the main ATSB trial. For the evaluation occurring during the main trial, these will be conducted at least 1-month after the introduction of the ATSBs. Focus group discussions (FGD) and in-depth interviews (IDI) will be conducted in intervention clusters (for the first evaluation, these will occur in areas where ASBs had been implemented for entomological validation trials) with the aim of understanding the potential factors influencing coverage. These qualitative methods will be applied as rapid ethnographic methods with a focus on rapidly available and actionable information to inform programmatic decisions. This includes guiding community engagement prior to the first ATSB deployment and informing strategies to ensure high community engagement and coverage levels throughout the trial. The FGDs will engage a set of community members as key informants in a discussion regarding community experiences with the ASBs and ATSBs. Separate FGDs will also be conducted with ASB and ATSB monitoring assistants serving as key informants on community experiences. The IDIs will be conducted with residents in intervention areas and will be used to explore in detail the experience of individual households with the ASBs and ATSBs. Additional messages will be created from these ethnographic methods to provide similar messages across arms to ensure LLIN usage and strengthen education and care-seeking behaviour for malaria.

9.1.7.1 *Procedures for focus group discussions*

1. Field workers will receive training in the study design, research tools, and study procedures for the FGDs and IDIs.
2. FGDs will be performed in each of the entomological validation clusters at baseline
3. ATSB monitoring data will be used during the main trial to classify clusters as having a relatively high or low incidence of ATSB damage, removal or replacement.
    a. Three clusters classified as high incidence and three clusters classified as low incidence will be randomly selected
    b. A single village within each of these six clusters will be randomly selected

4. Within each of the clusters/villages selected for FGDs, two groups of six to eight community members will be purposively selected by community-based field monitoring assistants based on their activity within the community and exposure to views and experiences of community members (i.e. school teachers, religious leaders, village elders)
5. Additionally, at each round, two sets of FGDs will be conducted with six to eight community-based ATSB monitoring assistants selected by the research team as key informants with monitoring ATSBs and deploying them
6. FGDs will be segregated by sex, and an equal number of FGDs with women and men will be conducted
7. Participants selected for FGD will be brought together in a central but private location and provided with an overview of the study and an informed consent form. Those that provide informed consent will continue to participate in the discussion.
8. The FGD will be closed to outside observers, limited only to consenting participants and the fieldworkers conducting the session.
9. Two field workers will conduct the FGD. One fieldworker will lead the discussion, and the other will take notes. The discussion will be recorded for transcription.
10. A semi-structured discussion guide will be used to guide the discussion (See separate file, ATSB Focus Group Discussion Guide (Community Members) and (Monitoring Assistants)).
11. The discussion will last approximately 60 minutes.
12. The recording of the discussion will be used to create a discussion transcript for data analysis.

9.1.7.2 *Procedures for in-depth-Interviews*

1. The first round of IDIs will be conducted among four key informants per each of the entomological validation and field trial study clusters. The four participants will be purposively selected using community-based field workers that assisted with the monitoring and implementation of the validation study. The field workers will be asked to select two households that experienced issues with the ASB, including damage, removal, or replacement, and two households that did not experience such issues.
2. One fieldworker will visit each selected potential IDI participant and will provide information about the study. The participant will be asked to provide informed consent. The interview will be conducted with people who provide informed consent.
3. The interviewer will use a semi-structured interview guide to guide a discussion that will last approximately 60 minutes.
4. The interview will be recorded for transcription.
5. The recording of the interview will be used to create a discussion transcript for data analysis.
6. Subsequent rounds of IDIs will be conducted during the trial. Twelve IDIs will be conducted within the 6 study clusters identified for FGDs as described above. Informants will be identified according to the procedures noted above. Within each cluster, the study team will seek one informant from a household that experienced ATSB issues and one informant from a household that did not experience these issues. The interviews will be conducted according to the procedures outlined above.

Data for FGDs and IDIs will be analysed thematically and may use software including Atlas.ti and NVivo for data organization and analysis.

9.1.8 Economic evaluation

ATSB product and delivery cost data will be collected and combined with efficacy measures of clinical malaria incidence to produce incremental cost-effectiveness ratios (ICER). The ICER will

represent the incremental cost-effectiveness of the use of ATSB in addition to standard of care malaria vector control (high/universal LLIN coverage) to estimate the financial and economic costs of the intervention. Cost data will be combined with efficacy estimates to produce cost-effectiveness estimates of this strategy from a provider perspective.

9.1.8.1 *Procedures*

Cost data collection will include a review of program records and reports, invoices, budgets, expenditure reports, as well as through interviews with intervention implementers to acquire information not recorded in existing program data. No interaction with study participants is required for provider perspective cost analysis. Interviews only with trial staff will be focused on resource use during the implementation of the study interventions. Where direct estimates of unit costs for inputs are not available through the above methods, data on costs will be supplemented with secondary source data such as is available from the WHO-CHOICE database, the World Bank, the International Monetary fund or other published literature. Economic costs will be estimated, meaning that costs from donated inputs will also be valued.

9.1.8.2 *Timeframe*

The collection of cost data will be conducted throughout the study period, with a review of cost data occurring quarterly throughout the scale-up and roll-out of the intervention and study. Final cost estimates and cost-effectiveness calculations will be done at the conclusion of the study.

9.2 DATA MANAGEMENT

The sections below provide details of data management for individual study components. All data will be stored on a secure, shared drive managed by KEMRI and backed up on a secure server at LSTM, Liverpool, UK. All investigators and the sponsor, IVCC, will have access to the data.

9.2.1 ATSB monitoring, cohort and cMIS case report forms

The questionnaire will be administered using electronic data capture forms on mobile phones or tablets. The data will be sent to a cloud-based secure server on a daily basis. Data will be extracted from the server after each round of ATSB monitoring is completed. The extraction will be completed using Alteryx, Microsoft Excel, or Microsoft Access, and data will be loaded into a package for statistical analysis such as Stata and/or SAS and/or R.

9.2.2 Passive case detection

Data entered into routine outpatient, ANC, and CHV MoH Registers will be extracted using ScanForm software and stored on a secure cloud-based server (under separate protocol).

9.2.3 Rapid ethnographic methods: FGD and IDI data

Transcripts of all discussions and interviews will be created in Microsoft Word. Interviews will be translated into English during the process of transcription. Data coding and analysis will be completed using Microsoft Excel.

9.2.4 Entomological monitoring

Field data will be recorded using electronic data capture forms on mobile phones or tablets. This will include details on the house structure (e.g., roof type, wall type, open or closed eaves), presence and use of LLINs, the timing of any IRS application within the last 12 months, and other factors that may affect mosquito density (e.g., cooking in the house, use of mosquito coils, presence of animals). Laboratory data will be entered using a standardized data entry form either directly on a PC or a

tablet. Data will be imported into Microsoft Access, and data merging, cleaning, and analysis will be done using a standard statistical software package such as SAS, Stata or R.

9.2.5 Economic evaluation

Data will be stored in the manner collected and collated into Microsoft Excel then transferred to R software for analysis. Transcripts of interviews with program staff will be created in Microsoft Word. All data will be backed up in a password-protected secure cloud storage setting to prevent data loss.

9.3 BIOLOGICAL SAMPLES

9.3.1 Blood samples

During cohort and cMIS household visits, a finger- or heal-prick blood sample (approximately 500 µL) will be taken to prepare dried blood spots (DBS) on filter paper. DBS will be used to evaluate malaria positivity or exposure through molecular and serological methods as well as exposure to mosquito biting at a later date and will not be used for clinical care. Should the participant be febrile at the time of the visit (axillary temperature ≥37.5°C) or report a fever in the previous 48 hours, a malaria RDT will also be performed. RDT results will be used for treatment decisions based on the Kenya Ministry of Health guidelines. In certain cases, to confirm parasite clearance, a blood smear may be prepared to perform light microscopy.

Real-time quantitative PCR will be performed on cohort samples to evaluate the time to first infection and may be performed on a sub-sample of cMIS samples to evaluate malaria prevalence. Should funds be available, PCR may also be performed to assess parasite genetics, including complexity of infection analyses to evaluate the impact of ATSB on circulating parasite strains.

Serological studies may be performed on cohort and cMIS samples to evaluate changes in exposure to malaria-associated with ATSB implementation as evaluated through antibody profiles of the participants. These may include IgG antibodies to antigens such as merozoite surface protein (MSP-1,) apical membrane antigen (AMA-1), circumsporozoite antigen (CSP), and other antigens. Additionally, exposure to vector biting may be assessed by measuring antibodies to mosquito saliva antigens, including Sg6 in the blood.

In other geographic areas such as Eritrea, HRP2 deletions have been identified. As the RDTs that are used in Kenya are based on HRP2 detection, the main trial outcomes rely on the detection of HRP2 antigens. Preliminary data from the study site (unpublished data 2018) have not identified evidence of HRP2 deletions. We may assess HRP2 concentration levels and PfHRP2/3 deletions from both cohort and cMIS samples.

9.3.2 Entomological samples

Collected mosquitoes will be returned to the laboratory for morphological identification, sporozoite ELISA testing, and, if necessary, species identification by PCR

9.3.3 Sample storage and shipping

9.3.3.1 *Storage*

All filter papers with DBS will be stored at the KEMRI CGHR campus in Kisian until the end of the study. All laboratory tests, as part of primary and secondary analyses, can be performed at the Kisian campus. For laboratory studies that may not be available at the Kisian campus, samples from participants who consent to shipment of samples may be shipped to laboratories at the CDC in the United States or to laboratories in the United Kingdom at the Liverpool School of Tropical Medicine.

For participants who consent, samples will be stored for up to 25 years from the time that the study ends. This is because the technology for sequencing parasites for clonal diversity, resistance, and serological markers of exposure is rapidly advancing. It may prove useful to analyze stored samples at a later date. At the end of the 25-year period, all biological specimens will be destroyed. Remnants of samples shipped to another laboratory will be destroyed after the testing has been completed.

9.3.3.2 *Shipping*

All specimens to be shipped will be packaged, shipped, and transported according to the current edition of the International Air Transport Association (IATA) Dangerous Good Regulations as at the time of shipping.

9.4 STATISTICAL METHODS

9.4.1 Interim analysis

9.4.1.1 *Purpose of the interim analysis*

The study is designed to have two interim and one final analysis, i.e. a total of three looks. The timing of the interim analysis is based on the number of cumulative events or person time accumulated as described in section 6.2.2, Duration of trial, interim analysis and criteria for early termination, page 17. In brief, the interim analyses will occur either after 50% and 75% of person-time have completed (i.e., after about 1 and 1.5 years respectively), or after 50% (n=372) and 75% (n=558) of the total number of expected primary outcome events over two years in the control arm (n=744) have occurred (whichever comes first).

The purpose of the interim analysis is to use the preliminary data to inform the assessment process by WHO's Vector Control Advisory Group (VCAG) in a timely manner. This requires at least a single year of data, but ideally, two years [18]. This study in Kenya is part of three similar trials conducted in Kenya (this protocol), Zambia and Mali. The combined results will inform WHO's recommendation process regarding ATSBs. Each of these three trials is designed to have an interim analysis. A decision to stop any of these three trials, including this one, early for overwhelming evidence of efficacy will depend on the overall evidence from the three trials and thus not only on the evidence generated from a single trial. It is thus possible that WHO's VCAG, the DSMB and/or the trial steering committee will recommend continuing this trial in Kenya for the full two years even if statistically the stopping boundary is crossed (suggesting overwhelming evidence of efficacy) or there is evidence of futility. The possible rationale for any of these committees to recommend continuing the trial for a second year may involve continuing collecting more epidemiological, entomological, behavioural, and safety information and data for further subgroup analyses. This would allow determining the cumulative effects of the intervention over a two-year period as behavioural changes of the population (e.g., change in adherence to the deployment of ATSBs), year-to-year seasonal variation in malaria transmission, cumulative impact on mosquito densities and community-effects, etc., may impact on the results over time.

However, it will also be possible that these committees recommend stopping the trial early if the committees agree that sufficient evidence is available after the first or second interim analysis to make a recommendation. This is the rationale to design the study to allow for two interim analyses.

9.4.1.2 *Procedures for interim analysis*

The interim analysis will be conducted on the primary endpoint using the intention-to-treat analysis population. First, the trial statistician will develop the analysis programs for the primary outcome

and validate them using a test version of the study database with a dummy random treatment code. Then, these programs will be provided to the DSMB statistician before the scheduled DSMB meeting. The DSMB statistician receives a copy of the random treatment assignment code directly from the study statistician or a second independent statistician not involved with the trial analysis. The DSMB statistician would replace the dummy random treatment code with the actual allocation code and execute the programs. Finally, after reviewing the analysis output and verifying the results, the DSMB statistician would summarize the findings in a report addressed to the other members of the DSMB.

9.4.1.3 *Evidence of benefit*

The interim analysis will consider the using the Haybittle-Peto spending function to determine the test boundaries to preserve the overall two-sided type I error rate of α=0.05 at the final analysis. Overwhelming evidence of benefit will be defined as a p-value favouring the intervention arm of <0.001 after the first or only interim analysis and also a one-sided p-value of <0.001 after the second interim analysis. This test will be conducted using a multilevel regression model with a Poisson likelihood and a log link function which includes random cluster level intercepts. Other models will be considered if there is evidence of overdispersion for Poisson (e.g. negative binomial models). The final null-hypothesis significance testing will be based on an alpha level of 0.049 to control the trial's overall type-I error potential.

9.4.1.4 *Stopping for harm*

The trials do not include formal stopping rules based on harm. The intervention is not targeted to humans, and the expected risk to trial participants is expected to be minimal. However, this does not preclude the DSMB from stopping the trial for harm should unforeseen consequences of the ATSB or trial procedures lead to harms.

9.4.1.5 *Timing of final analysis*

The final analysis will be conducted either following an interim analysis should the trial end early or at the end of two years should no early stopping rule be invoked.

9.4.2 General principles

9.4.2.1 *Analysis populations*

9.4.2.1.1 Intention-to-treat population

The primary analysis of the primary outcome (the incidence of clinical malaria in the cohort) will be conducted with the intention-to-treat analysis population, consisting of all eligible participants recruited and consented to participate in the study.

9.4.2.1.2 Per-protocol analysis populations

The per-protocol analysis populations will be those eligible, recruited, and consented participants whose cluster-level adherence meets the definition of adherence. Clusters (and those living in these clusters) will be excluded from the per-protocol population if they fulfil the criteria for non-adherence to ATSB deployment as defined in section 7.7.1, Cluster-level adherence, page 29. The ATSB monitoring data, which are contemporaneously collected, may be used to inform the further definition of the per-protocol population in the statistical analysis plan

9.4.2.1.3 Multiplicity

Whilst the trial tests multiple secondary outcomes, no adjustment will be made of multiplicity because the study has two arms and a single primary outcome. Secondary outcomes are assumed to be on the same causal pathway as the primary outcome.

9.4.2.2 *Missing data*

9.4.2.2.1 Missing outcome data

Significant effort will be made to reduce missing outcome data by revisiting cohort households multiple times and pre-scheduling follow up visits where possible. When missing data does arise due to failed monthly outcome assessment, no imputation will be used. Full reporting of the fraction of missing outcome assessments by study arm will be conducted for the intention-to-treat study population.

9.4.2.2.2 Missing co-variables

Missing baseline covariables (as defined in the SAP prior to data lock) will be imputed using simple imputation methods based on the covariable distributions, should the missing values for a particular covariable be less than 5%. For a continuous variable, missing values will be imputed from random values from a normal distribution with mean and SD calculated from the available sample. For a categorical variable, missing values will be imputed from random values from a uniform distribution with probabilities P1, P2, … Pk from the sample. The seed for the imputation will be set as a number with eight digitals (e.g. the date of the programming). If the missing values for a covariable are ≥5%, then they will be imputed using Markov chain Monte Carlo (MCMC) methods.

9.4.2.3 *Adjusting for cluster design and other correlated observations*

For all analyses, standard errors of effect estimates will be estimated with a random intercept at the cluster level to account for correlated observations at the cluster level as a result of the community randomized control trial study design.

9.4.3 Analysis of the primary outcome

9.4.3.1 *Definition of events and person-time to obtain incidence rates*

The primary outcome analysis will be based on a comparison of the unadjusted (crude) incidence rates between study arms using a multi-level (variance compartments model). The incidence rate will be defined as the total number of incident clinical malaria cases divided by the total person-time observed among each cohort.

The person-time (i.e., the denominator) and events (i.e., the numerator) will be defined as follows:

9.4.3.1.1 At the time of enrolment

If the blood smear collected two weeks after cohort enrolment (parasite clearance) visit is negative, person-time accrual will begin two weeks after enrolment to account for the post-prophylactic effect of the full treatment course with artemether-lumefantrine

9.4.3.1.2 After a positive RDT and malaria treatment

Similarly, two weeks of person-time will be subtracted after each treatment provided during the follow-up. This scenario would result in an event in the numerator

9.4.3.1.3 Visit following a positive malaria treatment

At the next visit (one month later), if the participant fulfils the criteria for clinical malaria (mRDT positive with symptoms), he/she will again be treated, and two weeks of person-time will be

removed. However, this will only be counted as an event (i.e. contribute to the numerator) if subsequent PCR testing for *P. falciparum* in the laboratory is positive. The rationale for this is based on the long tail of histidine-rich protein-2 (HRP2) antigenemia which can persist for weeks after active infections have cleared, resulting in false-positive mRDT results.

9.4.3.1.4 Visit where participant's overnight sleeping outside of the cluster of residence is documented

If a person sleeps outside of their cluster of residence for a period to be defined in the Statistical Analysis Plan based on a consensus between the three trials in Kenya (this protocol), Zambia and Mali, person-time and events for that month will be excluded. If the participant is found to be RDT positive, this event will not count in the numerator

9.4.3.1.5 Missed visits

Missing outcomes due to participant absence at scheduled visits will result in the removal of the previous period of follow-up time. Participants who return to the study after an absence of at least one measurement period and immediately test positive for clinical malaria will not be counted as cases, nor will their follow-up time between the last ascertainment and their return to study be counted (see section 9.4.2.2.1, Missing outcome data, page 46).

9.4.3.2 *Computing of incidence rate ratios*

To obtain incidence rate ratios, a multi-level variance compartments model will be used, constructed on a generalized linear model framework with a Poisson likelihood and a log link function. Random intercepts will be included for each study cluster, and study arm as a fixed effect coded categorically as 0 for arm A and 1 for arm B. The primary outcome will also be checked for the distributional assumption that the mean and variance of the outcome are similar after conditioning on cluster (e.g. are the within-cluster mean and variance similar). If the variance is substantially larger, a negative binomial likelihood will be considered. Results will be presented as the incidence rate ratio (IRR), 95% confidence intervals and *p*-value.

9.4.3.3 *Covariable adjusted analysis of the primary and secondary outcomes:*

A secondary co-variable adjusted analysis of the primary outcome will be conducted. Pre-specified covariables, developed and tested prior to final analysis, will be used. It is expected that these will also include the covariables used in restricted randomization (Table 4, below).

Table 4: Potential co-variables to be used in restricted randomisation

Variable	**Categorization (if applicable)**	**Analysis**	**Analysis Population**
Baseline prevalence	Calculated at cluster level	Clinical incidence, prevalence	ITT, per-protocol
Baseline incidence	Calculated at cluster level	Clinical incidence, prevalence	ITT, per-protocol
Rainfall (anomaly)	Summarized monthly at cluster level (lagged one month preceding) as anomaly	Clinical incidence, prevalence	ITT, per-protocol
Season		Clinical incidence, prevalence	ITT, per-protocol
Year	One vs Two	Clinical incidence, prevalence	ITT, per-protocol

Age	Under 60 months vs greater than 60 months	Clinical incidence, prevalence	ITT, per-protocol

9.4.3.4 *Subgroup analysis of the primary outcome*

We will perform a series of subgroup analyses that may include the list of subgroups in Table 5 below. Imputation for these baseline missing covariables (see section 9.4.2.2.2, Missing co-variables, page 46) will be carried out before categorizing. Assessment of the homogeneity of treatment effect by a subgroup variable will be conducted by the inclusion of the treatment, subgroup variable, and their interaction term as predictors in the adjusted models of the primary outcome and the *p*-value presented for the interaction term.

Table 5: Subgroups

Subgroup Name	**Categorization**	**Rationale**
Housing type	Closed eaves vs Non-closed eaves	House structure may act as an effect modifier by eliminating indoor biting risk independent of ATSB deployment
Gender	Male vs Female	The behavioural and occupational difference may act as an effect modifier
One month lagged rainfall (Total m per m^2 previous month)	High vs. low (>= mean for study site (country) vs. < mean for study site (country)).	High levels of absolute rainfall may reduce the impact of ATSB by increasing environmental carrying capacity for the mosquito population
Season	High vs low (four continuous months of the year with highest clinical malaria incidence at local health facilities during the trial) vs eight months with a lower incidence	(Kenya only)
Age	<= 60 months of age vs > 60 months of age, and possibly ≥15 years of age	Behavioural differences by age may act as an effect modifier

9.4.4 Other efficacy outcome analyses

9.4.4.1 *Analysis of secondary efficacy outcomes in the cohort*

9.4.4.1.1 Count outcomes

Similar methods of analysis will be used to obtain crude and adjusted incidence ratios for secondary clinical outcomes.

9.4.4.1.2 Time to first infection

The time to the first infection assessed among the cohort by PCR will be analysed using a Cox-proportional Hazards model. A shared frailty for study cluster and a 'fixed' effect coefficient for the study arm will be included. Results will be presented as the hazard ratio, 95% confidence intervals and p-values. The proportional hazards assumption will be checked using plotting and regressing the Schoenfeld residuals against time after model fitting. If the proportional hazards assumption is not

met, consideration of dose-response models with time-varying adherence measures will be considered, or alternative accelerated failure time models may also be considered.

9.4.4.2 *Analysis of the prevalence survey data*

The prevalence outcomes will be analysed using multi-level variance components models constructed on a log-binomial model with robust variance estimation. Random intercepts will be included for each study cluster, and the study arm will be included as a fixed effect. Model results will be presented as the risk ratio, 95% confidence intervals, and P-values.

9.4.4.3 *Analysis of the count data obtained by passive case detection*

The incidence data obtained from routine passive case detection in health facilities and through CHV in villages will be analysed using multi-level variance compartments models, constructed on a generalized linear model framework with a Poisson likelihood and a log link function. Random intercepts will be included for each study cluster, and the study arm will be included as a fixed effect. Denominator data to obtain person time for each cluster will be based on the enumeration data obtained from the census. Model results will be presented as incidence rates and incidence rate ratios, their associated 95% confidence intervals and p-value. Similar to the analysis of primary outcome, each count outcomes will also be checked for the distributional assumption that the mean and variance of the outcome are similar after conditioning on cluster (e.g. are the within-cluster mean and variance similar). If the variance is substantially larger, a negative binomial likelihood will be considered.

9.4.5 Analysis of entomological data

Mosquito densities will be analysed by Poisson or negative binomial regression using generalized estimating equations to adjust for correlated observations at the cluster level. Separate models will be done for each species where adequate numbers have been collected. All models will assume an auto-regressive correlation structure where the degree of correlation decreases with increasing time between collections. Models will include potential confounders such as the use of LLINs, recent house spraying, the presence of open eaves, and climatic factors. Logistic regression models will be used to compare the impact of ATSBs on binary outcomes such as the sporozoite rates, parity rates, the proportion of mosquitoes with three or more ovarian dilatations, or the proportion of outdoor biting. The logistic regression models will adjust for correlated observations at the cluster level using assuming an auto-regressive correlation structure.

9.4.6 Focus group discussions and in-depth interviews

Discussions during IDIs and FGDs will be recorded and subsequently transcribed. Qualitative data will be managed and analysed using directed content analysis whereby transcripts will be interrogated for specific and emergent themes. The interview guides and conceptual framework will be used to create an initial set of predetermined codes for the domains of potential barriers to high ATSB and LLIN coverage. Data will be coded and organized by theme and respondent type using Microsoft Excel or NVivo. Transcripts will be entered into an Excel file by transferring each codable unit to a separate cell on a line with additional cells containing information on the respondent (interview type, age, sex) for that unit of text. This process of data organization will allow the analyst to become familiar with the transcripts and refine the coding scheme as needed based on the data. Each unit of text will be assigned codes, and sub-codes entered in cells corresponding to the data. Excel Data functions, including Filter and Sort, will be used to organize data according to theme, review data within each assigned code, and make adjustments to coding. When coding is complete, a synthesis of data within each code will be drafted. Patterns among themes and across types of respondents will be identified and interpreted.

9.4.7 Economic evaluation

Both financial and economic costs will be calculated. Costs will be classified as capital or recurrent and traded vs non-traded. Capital costs will be annuitized and discounted using a 3% rate. These costs will be expressed in a common currency and year (2019 US dollars). Additionally, they will be converted into purchasing power parity adjusted International Dollars for internal comparison. Costs will be combined with efficacy measures from the trial to estimate incremental cost-effectiveness measures.

9.4.8 Harms

The main risks associated with the intervention are the risk of physical contact or ingestion of the bait by humans, animals, and/or non-target arthropods, particularly the local bee population. Continued entomological monitoring of non-target insect populations and ongoing monitoring of trial sites for misuse or product loss will be conducted. The statistical analyses of harms to study participants will consist of evaluating the number of AEs and SAEs related to physical contact or ingestion of the bait. analysed

10 METHODS: MONITORING

10.1 TRIAL GOVERNANCE

10.1.1 Trial steering committee

The ATSB project is governed by a steering committee with members from the Bill and Melinda Gates Foundation, IVCC, Westham Co., PATH, the University of Bamako, and two external expert advisors (one epidemiologist and one entomologist). The steering committee meets quarterly to discuss all aspects of the project, including study protocol and procedures, additional external reviews and reviewers (e.g. WHO VCAG), product and production issues, timeline and deliverables, and review of available data.

10.1.2 Data safety and monitoring committees

An independent data safety monitoring board (DSMB) will be established to monitor implementation. The board will consist of at least four independent experts in malaria vector control, entomology, the conduct of community trials, biostatistics, and epidemiology. The members of the DSMB will serve in an individual capacity and provide their expertise and recommendations. No independent member of the DSMB shall have any conflict of interest with the study team, the organizations funding or conducting the research, the results of the research, or the ATSB manufacturer (Westham Co.).

The primary responsibilities of the DSMB will be to periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy. The DSMB will be responsible for making recommendations to investigators and participating in research ethics committees concerning the continuation, modification, or termination of the trial. The DSMB will be guided by a charter. This charter will include statistical monitoring guidelines that will guide recommendations about the trial's termination or continuation. These procedures will include guidelines for termination for futility and termination for safety reasons (see Section 9.4.1, Interim Analysis, page 45).

10.2 TRIAL MONITORING AND AUDITING

10.2.1 Trial monitoring

External clinical trial monitoring visits are provided by the sponsor at trial initiation, and then regularly (at least yearly) thereafter and at trial closeout, or more frequently if so required; e.g. if the trial fieldwork is about 24 months, this means that the site is visited approximately four times by external monitors. The results from each monitoring visit will help inform whether more frequent or earlier repeat visits are required.

10.2.2 Auditing

The independent trial monitoring process will be audited by a study staff from the sponsor's research office at LSTM in Liverpool, UK. The auditor may choose to accompany the clinical monitor during at least one of the site visits to determine if more auditing visits are required.

10.2.3 Role of sponsor

The sponsor reserves the right to suspend temporarily or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. If the sponsor determines such action is needed, it will discuss this with the investigator and the funder (IVCC). When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect. The sponsor will promptly inform the ethics committees and provide the reason for the suspension or termination.

10.3 SAFETY MONITORING AND REPORTING

10.3.1 Adverse events and serious adverse events

Adverse events (AEs) and serious adverse events (SAEs) will be recorded in the study cohort during home visits and sick visits. Since this is not a trial involving a human intervention, these AEs and SAEs will not be reported in an expedited manner to the DSMB, sponsor, ethics committee or regulator. The exceptions are AEs or SAEs related to a physical interaction with ATSBs or ingestion of ATSB materials. Any ingestion of ATSB material will be considered an event that requires expedited reporting regardless of the seriousness of the event. Thus both SAEs or AEs related to physical interaction with ATSBs or ingestion of ATSB materials will be reported by the principal investigator to the DSMB, sponsor and ethics committee/institutional review boards within 72 hours. Study staff will be trained to report such events to the principal investigator in an expedited manner. Participants will also be instructed to contact the study staff if ingestion were to occur. All other AEs and SAEs not related to a physical interaction with ATSBs or ingestion of ATSB materials will be reported at the time of continuing review.

10.4 QUALITY ASSURANCE

10.4.1 Quality assurance field-based activities

Field coordinators will be employed to provide supervision to all field staff and ensure that human blood and mosquito specimens are collected, transported, and stored according to standard operating procedures.

Additional staff will support passive routine data collection at health facilities. (see Section 9.1.4, Passive case detection, page 37)

10.4.2 Quality assurance data

10.4.2.1 *Routine review of ATSB monitoring data*

The ATSB monitoring data will be reviewed on an ongoing basis (minimum quarterly basis) to assess the extent to which full coverage with ATSBs is achieved in intervention areas. This information will be used to take necessary action to address gaps in coverage.

10.4.2.2 *Routine review of cohort data quality*

The cohort data will be reviewed on an ongoing basis (minimum quarterly basis) to assess data quality. Checks will be performed to ensure data completeness and assess consistency. Information from these data reviews will be used to take action to address data quality issues as needed.

10.4.2.3 *Continuous household survey data review*

The household survey data will be reviewed for data completeness and consistency. Information from these data reviews will be used to take action to address data quality issues within the continuous household survey to ensure a minimum level of quality.

10.4.2.4 *Routine review of health facility data*

The passive case detection data collected at health facilities will be reviewed on an ongoing basis (minimum quarterly basis) to assess data quality. Checks will be performed to ensure data completeness and assess consistency. These checks will include ensuring that the geographic location of cases is being recorded sufficiently to assign each case to the correct study arm. Information from these data reviews will be used to take action to address data quality issues within the passive case detection collection at facilities.

10.4.2.5 *Review of qualitative study data*

Data from each of the two rounds of qualitative data collection will be analysed as data become available. Results from these studies will be used to address barriers to continuous coverage with ATSBs and LLINs (i.e. strengthened and targeted community engagement strategies).

10.4.2.6 *Review of ATSB durability monitoring and insecticide resistance monitoring data*

Results from data collection to monitor ATSB durability and insecticide resistance will be analysed and reviewed as these data are collected. Results from these study components will be used to flag and address unanticipated issues with shorter than anticipated ATSB product life in the field (less than six months durability of the attractant and ingestion toxicant) and/or evidence of target vector resistance to the ATSB active ingredient.

10.4.2.7 *Routine review of entomological monitoring data*

The entomological monitoring data collected monthly will be reviewed on an ongoing basis (minimum quarterly) to assess data quality. Checks will be performed to ensure data completeness and assess consistency. Information from these data reviews will be used to take action to address data quality issues within entomological data collection and entry.

10.4.2.8 *Midterm analysis of entomological monitoring data*

The entomological monitoring data will be analysed after one year to examine trends in key entomological indicators, including trends in density and population age structure in intervention and control areas. Should this analysis suggest no entomological effect of the intervention, a comprehensive review of trial procedures, intervention coverage, contextual information (e.g. weather and rainfall trends), and data quality will be undertaken.

10.5 DATA COLLECTION METHODS & STORAGE

10.5.1 Methodologies for data collection/generation

Data will primarily be captured using mobile data collection tools such as tablets and smartphones. Routine MoH register data are collected on paper-based forms utilising ScanForm (QED®) software for semi-automated transcribing into an electronic database by taking images with android-based ScanForm App and using Optical Character Recognition, intelligent document recognition and data validation and human verification of information against source documents. Once validated, the data will be transferred to the target database along with a PDF of the original image of the CRFs, such that there is an electronic copy of all paper-based documents. For the electronic-only data capture, we will use tablets with integrated sim cards to transfer encrypted data to the ODK servers. This has worked well in previous studies.

10.5.2 Data quality and standards

The quality of questionnaire data collection and data entry will be maximised through the training of field staff in the standardised questionnaire administration methodology. Field staff will be trained in the methodology for collecting data and will be expected to demonstrate competence before conducting fieldwork

10.5.3 Managing, storing, and curating data

Verified and validated data will be stored on secure, highly fault-tolerant, storage area network servers. Locally, data will be backed-up on a continuous basis on a secure off-site server and on encrypted standalone hard drives.

Once the data validation phase is completed by the central data manager, the database will be locked and transferred to a statistical programmer who will do further syntax-driven consistency checks and syntax-driven data cleaning. The statistical programmer will have access to the source data. He/she will then prepare the database for data analysis by the statistician by creating the final variables for data analysis, such as the creation of the composite endpoints. The final cleaned database will be available in Stata, SAS, R and other formats, with a corresponding data dictionary.

10.5.4 Data preservation strategy and standards

The majority of the data collected will be captured using electronic data collection tools such as tablets or smartphones. The country-specific paper-based ICFs and the databases will be stored and archived at KEMRI's Centre for Global Health Research (CHGR) in western Kenya. The research data will be stored in the long-term in the original electronic format, in a large unified database and a public database that contains all research data other than identifiable participant data. The public database will be updated when needed if the software becomes obsolescent to achieve long-term preservation. The data will be preserved in this way for ten years or longer if still being accessed at that stage.

11 ETHICS AND DISSEMINATION

11.1 DECLARATION OF HELSINKI

This study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP, and in accordance with all applicable regulatory requirements in Kenya.

11.2 RESEARCH ETHICS AND REGULATORY APPROVAL

11.2.1 Ethical review and approval of study protocol

This protocol will be reviewed by the research ethics committee and institutional review boards at the KEMRI and LSTM. A reliance agreement based on KEMRI's review will be submitted to the CDC.

11.2.2 Protocol amendments

No changes will be made to the approved protocol without the agreement of the sponsor, Chief Investigator and Principal Investigators. All protocol amendments will be submitted to the research ethics committees at LSTM (sponsor) and KEMRI for approval before implementation in that country. Any change to the informed consent form, except for layout, spelling errors and formatting, must also be approved by the sponsor and KEMRI before the revised forms are implemented.

11.2.3 Regulatory approval

Additionally, this study will be submitted to the National Commission for Science, Technology & Innovation (NACOSTI) and it will be registered with ClinicalTrials.gov. Import permits will be sought from and the Kenya Pest Control Products Board (PCPB) for ATSB shipments to the study site.

11.2.4 Inclusion of vulnerable subjects: children and pregnant women

The cohort study will include children age 1-<15 years. Informed consent from the parent or guardian will be obtained before participants are enrolled. Additional assent will be obtained for children age 13-<15 years (see 11.2.5, Consent procedures, below) per local guidelines.

Pregnancy is an exclusion criterion because enrolment in the cohort requires presumptive clearance of any existing infections with artemether-lumefantrine. WHO does not yet recommend artemether-lumefantrine for the case-management of confirmed malaria in the first trimester, nor does it recommend the presumptive treatment with ACTs at any time during pregnancy. It is possible that some girls aged 12-<15y could be pregnant. Pregnancy will be excluded by asking girls aged 12-<15y about their date of last menstrual period. If this is >=6 weeks, she will be asked if she could be pregnant. If she is unsure, a urine human Chorionic Gonadotropin (hCG) rapid pregnancy test will be offered. Any girl who is unsure about her pregnancy status and is hesitant to do a urine-based hCG pregnancy test will not be eligible for enrolment. Any study participant who is pregnant at screening or becomes pregnant during the study will be referred to the antenatal clinic for further follow-up and care.

11.2.5 Consent procedures

11.2.5.1 *Consent and assent*

Written informed consent will be sought for all participants aged >= 18 years. For participants aged <18 years of age consent from the parent/guardian will also be required. Additional assent will be obtained for children age 13-17 years (13-<15 years in the cohort study, 15-17 in the in-depth interviews). Table 6 below summarises the consent/assent forms for each study component.

The informed consent forms will consist of a participant information sheet (PIS) and a consent/assent statement for their signature or thumbprint. The consent/assent process will be initiated at the time of enrolment into the study and will continue throughout the participant's participation. If the participant meets the study enrolment criteria following an initial screening for basic eligibility criteria, the full consent process will follow. The consenting/assenting procedures will be conducted by trained staff who will answer any questions the participants may have. Participants (and if applicable based on Table 6, their parent/guardian) will be given the option of reading the PIS

in the local language, having the PIS read to them in the local language, or both. The PIS's include a description of voluntary participation, the right to withdraw from the study at any time without having to give a reason, and the right not to answer specific questions or participate in a specific component of the research. The participant information sheets also address the risks, benefits, and purpose of the study.

Table 6: Consent and assent for each study component

Study component	Inclusion ages	Written consent/ assent
ATSB installation	18 years and older	• Consent
Cohort study	1-12 years	• Parent/guardian consent
	13-14 years	• Parent/guardian consent • Child assent
Focus group discussion	18 years and older	• Consent
In-depth interview	18 years and older	• Consent
	15-17 years	• Parent/guardian consent • Child assent
Entomological monitoring (light traps at household level)	18 years and older	• Consent
Entomological monitoring (HLC)	Males, 18 to 49 years old	• Consent

No informed consent or assent will be sought for the passive surveillance studies as no identifiable data will be collected. The continuous malaria indicator household survey (cMIS) falls under a separate approved protocol (SSC #2773; LSTM Protocol #14.009; CDC Protocol #6733).

Participation in the research study is voluntary. Participants refuse the installation of ATSBs on the exterior walls of their house. Participants electing not to participate in other components of the study may still receive ATSBs as part of the intervention.

For illiterate participants, an independent witness will be present during the informed consent process. Any adult aged 18 or older who is independent (e.g. a family member, neighbour etc) may act as a witness for the consent of illiterate participants. The witness will sign the consent form, while the participant or their parent/guardian will be asked to indicate consent by use of a thumbprint.

A copy of the informed consent/assent document will be given to the participant and their parent/guardian for their records. Each consent statement will be co-signed by a staff member. A signed consent statement will be forwarded to a central location for storage within a secured cabinet under lock and key. Checks in the field by the principal investigator and project leaders will further ensure that the consent process is followed.

11.3 RISKS AND BENEFITS

11.3.1 Risks to study participants

11.3.1.1 *Exposure to insecticide*

The active ingredient in the ATSB, dinotefuran, is an insecticide manufactured by Mistui Chemicals Agro, Inc. in Tokyo, Japan. Dinotefuran is a neonicotinoid insecticide that is effective for mosquito control. The ATSB contains 100 grams of the sugar/fruit juice solution and 0.1% dinotefuran (0.1 gram). The safety data sheet is provided in Annex I. Dinotefuran safety data sheet, page 68. A study of human health and environmental risk for dinotefuran deployed within the Westham Co. ATSB was commissioned in 2017. The results are provided in Annex IV: ATSB human and environmental safety

assessment report, page 109. Briefly, the assessment found that the use of dinotefuran in ATSBs under normal conditions of use is not expected to present an unacceptable risk to users handling the product or to residents living in the community. The human health risks of potential exposure to dinotefuran are considered low. In the worst-case assessment whereby a child would get ahold of one or more products and deliberately break them open to ingest the sugar bait, ingestion of the contents of an entire ATSB is unlikely to lead to a significant poisoning incident. In fact, under the most conservative assumptions regarding human toxicity, a child consuming 20 bait stations may experience severe poisoning. However, the assessment deemed this highly unlikely.

Given the amount of dinotefuran-laden bait required to induce severe poisoning based on weight, an acute poisoning event among livestock or other domesticated animals is highly unlikely. The risk to animals would be an issue if an animal such as a goat or dog would ingest the bait from hundreds of stations.

To address the potential consumption of bait by humans or animals, Westham incorporated a widely used bittering agent called Bitrex into the bait. Bitrex (denatonium benzoate) is an additive for a number of household products in order to prevent a poisoning event (see Annex II: Denatonium benzoate safety data sheet, page 75 for more information).

11.3.1.2 *Risks associated with blood sampling*

Table 7 below outlines the risks associated with each component of data collection. A primary risk associated with data collection is the risk involved in a finger/heal-prick for blood draws for malaria RDTs and dried blood spots. Finger and heal-prick blood draws can cause pain and redness or swelling at the finger or heal-prick area and carry a risk of infection at the site of the lancet puncture.

11.3.1.3 *Risks associated with the protection of privacy and confidentiality*

Collection of household and individual identifying information is necessary for the follow-up procedures. Geolocations of all households involved in the intervention and surveys will be collected. The collection of this information poses a potential threat to the confidentiality of individual data. Interview forms will contain little information that would generally be considered to be sensitive. Notably, there is no stigma associated with malaria infection status in the study communities. However, there is a risk that the privacy of an individual could be compromised during the administration of a questionnaire.

Table 7: Risks associated with each type of data collection

Type of data collection	Description	Risk
Census enumeration	Household questionnaire	No risk
ATSB monitoring	Monitoring visit once every two months to confirm installation and assess the condition of the ATSB	No risk
Cohort study enrollment and monitoring	Brief questionnaire Fingerstick for RDT and dried blood spot collection	Minimal risk from the finger stick Side effects of malaria treatment Inadvertent pregnancy disclosure
Household survey	Household questionnaire Fingerstick for RDT and dried blood spot collection	Minimal risk from the finger stick

		Side effects of malaria treatment Inadvertent pregnancy disclosure
Focus group discussion	Semi-structured group discussion with recording and transcription of the conversation	No risk
In-depth interview	Semi-structured interview with recording and transcription of the conversation	No risk
Entomological monitoring	Mosquito traps will be placed inside and outside of homes and will trap mosquitoes during peak biting hours beginning in the early evening through the early morning.	No risk
Entomological Monitoring	Indoor and outdoor human landing catches through the night	Minimal risk of mosquito bites and malaria infection
Economic evaluation	Collection of intervention cost data	No risk

11.3.2 Risks to the population or environment

The main environmental concern with the use of dinotefuran is the potential harm for non-target arthropods such as bees which are known to be sensitive to neonicotinoids like dinotefuran. The assessment summarizes a feeding study that examined feeding rates using a sample of over 3,700 species from 7 orders and 27 suborders. The percentage of dissected samples that fed on the bait stations was shown to be very low, ranging from 0-2%. The study concluded that the ATSB design effectively limits exposure of the treated bait to non-target arthropods (see Annex IV: ATSB human and environmental safety assessment report, page 109).

According to a US EPA fact sheet (https://www3.epa.gov/pesticides/chem_search/reg_actions/registration/fs_PC-044312_01-Sep-04.pdf), dinetofuran is water soluble and has a potential to leach into subsurface soil layers and/or enter rivers, ponds or lakes through surface runoff. However, dinetofuran is considered practically non-toxic to birds, mammals and fish on an acute basis though there were subacute effects on Japanese quail and mallard ducks including reduced numbers of eggs laid and reduced 14-day old survivors. Chronic toxicity testing on freshwater invertebrates showed no effects.

Although there appears to be limited risk of effects on non-target organisms other than insects due to accidental release of dinetofuran into the environment, we will take measures to limit such releases. First, the dinetofuran is contained within a bait station and only limited amounts are available to insects with piercing mouthparts (i.e. mosquitoes). The main risk for accidental release is through damage to the bait stations or misuse by residents that receive them. To minimize this, we will educate residents who receive bait stations on the importance of keeping the ATSBs on the exterior walls, both for the validity of the study and to protect against harm to people or the environment. We will instruct residents to contact a study staff member in the event an ATSB is lost or damaged. Second, we will conduct periodic spot checks on the bait stations and document the risk of accidental loss or intentional misuse. Last, we will collect ATSBs after six months before replacement with new ones. If, at any time, excessive damage or loss is observed, additional measures will be implemented to minimize the risk of future damage/loss of the ATSBs.

11.3.3 Adequacy of protection against risk

11.3.3.1 *Protection against risks associated with exposure to the insecticide*

As outlined in Section 11.3.1, Risks to study participants, page 55, the main risks associated with the intervention are the risk of ingestion of the bait by humans, animals, and/or non-target anthropods, particularly the local bee population. The following measures will be taken to minimize the risk of exposure for all non-target organisms to the bait:

- ATSBs will be installed by trained monitoring assistants to ensure the proper installation of all ATSBs released into the community. The ATSB monitoring assistants will visit each household at least one time every month to verify that all ATSBs remain properly installed and will inspect the ATSBs for damage. Damaged ATSBs will be removed and replaced by the ATSB monitoring assistants. The ATSB monitoring assistants will attempt to recover and will safely dispose of any ATSBs (see below) that are not present at the time of the monitoring visit or that are reported missing by a participating household.
- ATSBs will be replaced every six months. The ATSB monitoring assistants will remove the ATSBs, and a field supervisor for disposal will collect all ATSBs to ensure that the products do not remain in the community. ATSBs will be incinerated in a high-temperature incinerator.
- Based on previous field research in Mali, manufacturer guidelines stipulate installing the ATSBs at a height of 1.8 meters. This is intended to minimize access to the bait from children and animals. This was shown to be successful in Mali (unpublished data). ATSBs will be installed at this height in all trial sites.
- Unused ATSBs and ATSBs that have been removed and are awaiting incineration will be stored in secure locations that prohibit access by children and animals. Conditions of storage may include rooms with locked doors and covered windows (glass, wood, metal, or screen covers) or locked boxes.
- Community sensitization activities will be implemented before and during the initial ATSB installation. These may include radio spots and presentations at community meetings that will include information on proper installation of ATSBs, instructions to keep ATSBs out of reach from children and animals and remove and report damaged ATSBs. It will also include contact information for community-based resources that can provide more information and assist with damaged or missing ATSBs.
- An informed consent form will be administered to all participants in the local language at the time of the ATSB installation. ATSBs will only be installed at households where the head of household or his/her representative provide consent. The information provided at the time of installation will include an overview of the potential risks to non-targets and instructions to 1) maintain the installation of the ATSBs at the height of 1.8 meters; 2) inform the contact provided (community-based ASTB monitoring assistant) should the bait station become damaged, missing, or if assistance is required to reinstall the bait station; and 3) to keep the ATSB away from the children and animals should the intended, or unintended removal of the bait station occur and if so, contact the community-based ATSB monitoring assistant (contact information provided).

11.3.3.2 *Protection against the risks associated with blood sampling*

Trained and experienced staff will be used for the administration of the malaria RDT and collection of DBS. These health workers will follow detailed standard operating procedures designed to minimize the risk of pain, redness, swelling, and infection.

An informed consent form will be administered to all participants in the local language for participation in each component of the study.

11.3.3.3 *Protection of privacy and confidentiality*

Confidentiality of participant data and privacy of the participants will be preserved through the following measures:

- Interviews and testing will be conducted in a private place within the participant's homestead.
- Focus group discussions will be closed to outside observers and will be held in a private location.
- Fieldworkers will receive training to maintain privacy during interviews and blood testing and preserve the confidentiality of all information collected.
- Identifying information will be recorded only in secure database software on password-protected smartphones or tablets. Field workers will only have access to the data that they directly collect. Data will be cleared from their devices after all follow-up visits are complete. Data will be compiled by field supervisors or sent directly via secured mobile connections to central servers and will be stored only on password-protected computers in locked offices.
- Prior to data analysis, the data will be de-identified except for geo-location codes which are necessary for specific per-protocol analyses. The absence of individual identifying information will protect subject confidentiality.
- All paper records and blood specimens (DBS) will be stored in a locked location.

11.3.4 Potential benefits of the research to participants

Participants will directly benefit from the top-up distribution of LLINs to ensure universal coverage throughout the study area. Furthermore, participants in the intervention area may benefit from the community-wide reductions in malaria transmission that are hypothesized to occur with the ATSB intervention. Participants in the study cohort will benefit from monthly testing and treatment for malaria infection. Participants in the household survey will benefit from malaria testing and treatment.

Participants may also indirectly benefit as the information gained from this research will be used to inform a WHO recommendation regarding the use of the ATSB to further reduce malaria transmission above and beyond reduction achieved through universal LLIN coverage. The research will benefit the scientific and malaria control communities more generally by providing evidence on the efficacy of the ATSB as a potential tool to address residual malaria transmission. These types of new tools will be required to continue reducing malaria transmission and ultimately achieve elimination. Ancillary and post-trial care

11.3.5 Health care during the trial

Care directed to immediate adverse events related to trial procedures (such as taking biological samples) will be provided free of charge by the study in the study hospitals. For cohort participants, care will be provided to evaluate, diagnose and treat acute illness. The study will not be able to support care for trauma or chronic illness that was existing prior to or after the commencement of the study that cannot, in any way, be reasonably attributed to trial participation. The intervention is targeting the vector and is not anticipated to have an impact on participants.

11.3.6 Trial insurance

The sponsor will take out trial insurance such that participants enrolled in the intervention study are covered by indemnity for negligent harm and non-negligent harm associated with the protocol. This will include cover for additional health care, compensation or damages whether awarded voluntarily by the Sponsor or by claims pursued through the courts. The ATSB manufacturer's liability is limited to claims arising from faulty manufacturing of the commercial product and not to any aspects of the study conduct.

11.3.7 Post-trial care

The study budget is not able to fund post-study care or implementation of ATSBs. However, the investigators work in close collaboration with local and international policymakers (e.g. WHO) and funders (e.g. President's Malaria Initiative [PMI]) to ensure that policymakers and funders are informed early of germane research findings. If the evidence supports the efficacy of the ATSB, we will advocate with the Division of National Malaria Programme and its partners, including PMI, for continued implementation of the ATSBs in intervention and control areas with supportive monitoring and disposal.

11.4 Declaration of interest

None of the investigators has paid consultancies with the companies involved in the trial or other competing interest for the overall trial or in each study site.

11.5 Access to source data/documents

In addition to the clinical monitors, authorized representatives of the funder, sponsor/CRO, an IEC/IRB, or regulatory authority may visit the study site to perform audits or inspections, including source data verification. The investigator agrees to allow the sponsor and CRO representatives, including the monitor and study safety monitor, the DSMB, the IRB/IEC and regulatory authority, direct access to source data and other relevant documents.

11.6 Expenses reimbursement and other payments to participants

No payment for household visits will be provided to participants. A transport reimbursement of 400 Kenya shillings will be provided for sick visits when a parent/guardian must travel to a clinic to see study staff. Those who participate in human landing catches (HLCs) will be compensated up to 1000 Kenya shillings for their time.

11.7 Dissemination and application of the results

The purpose of this study is to provide a body of evidence to the VCAG in order to make a recommendation on the use of ATSBs in the year 2022. Data from this study will be combined with data from two other study sites where a similar protocol is being implemented. The outcome of these studies will guide recommendations for implementation or further testing to be performed on the Westham Co. ATSB product. The findings of this study will be directly applicable to western Kenya as this is an area of high malaria endemicity with presumed outdoor biting for which the ATSBs were specifically designed to be deployed.

After study completion, study staff will hold "barazas" (town halls) and other community meetings within the involved counties to present the results of the study.

11.8 AUTHORSHIP AND PUBLICATIONS

Potential authors include all professionals that have participated in the trial for a minimum of six months. Authorship of any presentations or publications arising from this study will also be governed by the principles for authorship criteria of the International Committee of Medical Journal Editors has designed.[22] Disputes regarding authorship will be settled by the publications committee, with further involvement of the independent chair of the TSC if so required. The manufacturers of the ATSBs will be provided with a draft of the manuscript but will have no role in the review, data interpretation, or writing of the article.

11.9 DATA SHARING STATEMENT

Biological samples and data will be shared using material and data transfer agreements with the collaborating institutions (see 2.2.4 Non-Engaged collaborators, page 7) to minimize the risk of unauthorized analysis beyond the scope of the agreed parameters.

The full protocol will be available on request to any interested professional and may be published in a peer-reviewed journal or deposited in an online repository. Individual, de-identified participant data will be made available for meta-analyses as soon as the data analysis is completed, with the understanding that the meta-analysis results will not be published before the individual trial results without the prior agreement of the investigators. The de-identified data set of the complete participant-level data will be available for sharing purposes, such as via the WWARN repository platform (http://www.wwarn.org/working-together/sharing-data/accessing-data). A Data Access Committee will consider all requests for data for secondary analysis to ensure that the use of data is within the terms of consent and ethics approval.

12 TIMEFRAME AND DURATION OF THE STUDY

Table 8 summarises the timeframe for each study component.

Table 8: Timeline

	2021				2022				2023				2024	
	1	2	3	4	1	2	3	4	1	2	3	4	1	2
Qualitative study														
Launch of community engagement														
Baseline Passive Surveillance														
Baseline Household Survey														
Baseline Cohort														
LLIN distribution														
ATSB installation (every 6 months)														
Collect ATSBs for disposal														
Main Trial Passive Surveillance														
Main Trial Household Survey														
Main Trial Cohort														
Final Reporting														

13 ROLES OF THE INVESTIGATORS

13.1 INVESTIGATORS

Dr Aaron Samuels is the Director of the CDC-Kenya Malaria Research Program based in Kisumu, Kenya. He will serve as the co-PI on this study, with a particular focus on the epidemiological aspects of the study. He will be engaged with participants and will have access to personally identifiable information. He will be responsible for the local design, methodology, and conduct, and the analysis and reporting of the study. He will provide coordination and technical advice to the epidemiology staff and serve as a liaison to the non-engaged collaborators and other institutions.

Dr Eric Ochomo is the KEMRI-CGHR Entomology Section Head in Kisumu, Kenya. He will also serve as a co-PI on this study, with a particular focus on the entomological aspects of the study. He will be responsible for the local design, methodology, and conduct and the analysis and reporting of the study. He will provide coordination and technical advice to the entomology staff and serve as a liaison to the non-engaged collaborators and other institutions.

Dr Feiko ter Kuile is a Professor of Tropical Epidemiology at LSTM and is based part-time in Kisumu, Kenya. He will be the Chief Investigator of this trial and provide technical advice and support pertaining to study design, methodology, conduct, analyses, and manuscript writing.

Dr Simon Kariuki is the KEMRI-CGHR Malaria Branch Chief and Chief Research Officer in Kisumu, Kenya. He will provide high-level technical support to the epidemiological, entomological and laboratory components of the trial design, methodology and conduct. He will also play a supervisory role.

Dr John Gimnig is an Entomologist in the CDC Entomology Branch in Atlanta, GA, USA. He will provide higher-level technical advice and support as it pertains to the entomological study design, methodology, conduct, analyses, and manuscript writing. Dr Gimnig will also provide on-ground technical support to staff.

Kephas Otieno is the KEMRI-CGHR Malaria Laboratory Section Head. He will provide technical oversight to the laboratory components of the study, including the methodology and implementation of these components.

Benard Abong'o is an entomologist working for the KEMRI-CGHR Entomology Section of the Malaria Branch. He will provide study coordination and responsibilities and technical advice towards the design, methodology, and implementation of the entomological components of the study.

Dr Julia Janssen is a medical doctor and Epidemic Intelligence Officer Fellow at the US CDC. She will assist with local design, methodology, and conduct, and the analysis and reporting of the study. She will be engaged and provide coordination and technical advice to the epidemiology staff and serve as a liaison to the non-engaged collaborators and other institutions.

Dr. Caroline Ogwang is a Medical Doctor at KEMRI. She will serve as the Trial Manager for the epidemiological aspects of the trial. She will be engaged in trainings and direct supervision of staff, and ensure that the protocol and SOPs are followed. She will be involved in data analysis, report writing, manuscript preparation and dissemination of findings. She will also coordinate communications between the engaged and collaborating institutions as well as the Kenya Ministry of Health.

Dr. Maia Lesosky is PhD in biostatistics and will serve as the site-specific statistician for the ATSB trial in Kenya. She will be involved in development of the statistical analysis plan, data cleaning, analysis and report and manuscript development.

Dr. George Okello is a PhD level behavioural scientist. He will be leading the qualitative components of the trial including assisting with the development of the methodology, conduct, analyses and report writing. He will be providing direct and technical oversight and supervision of the staff implementing the qualitative components.

13.2 Non-Engaged Collaborators

Kennedy Odhiambo Oruenjo is the County Director of Public Health, Sanitation and Health Planning for Siaya County, Kenya. He will provide critical communications with the study, the ministry, other programs working int eh study area, as well as the communities. He will assist with community sensitization and acceptance. He will additionally assist with study findings and interpretations for dissemination, including manuscript and presentation dissemination.

Dr Megan Littrell is an Epidemiologist with PATH based in Washington, D.C., USA. She will provide technical advice into the overall study design, methodology, conduct, analyses, and manuscript writing. She will also serve as the liaison with the DSMB, Trial Steering Committee, VCAG, IVCC and Westham Co.

14 Financial aspects and conflict of interest

14.1 Funding for the trial

This study is funded by the Innovative Vector Control Consortium (IVCC) based in Liverpool, UK, which is funded by the Bill & Melinda Gates Foundation.

IVCC provided support in the design of the trial through their independent expert scientific advisory committee. Support was also provided by the Design, Analyze, Communicate (DAC) team from the Bill & Melinda Gates Foundation. Guidelines provided by WHO's Vector Control Advisory Group (VCAG) were also taken into account in the design of the study.[18]

IVCC will reserve the right to review any draft manuscripts of the trial but will not have any role during the execution, analysis, interpretation of the data.

14.2 Provision of ATSB

ATSB will be provided by Westham Co., Israel.

14.3 Budget

14.3.1 Budget table

Table 9: Budget		
Description	Cost KSH (100 KSH to 1 USD)	Cost USD
Personnel	214,883,682	$2,148,836.82
Supplies	84,783,550	$847,835.50
Equipment	2,750,000	$27,500.00
Other Direct Costs	34,175,747	$341,757.47

Travel	23,155,552	$231,555.52
Subtotal	359,748,531	$3,597,485.31
Total Indirect Costs 15% (to KEMRI and LSTM UK)	53,962,280	$539,622.80
Total	413,710,811	$4,137,108.11

14.3.2 Budget justification

The overall budget includes the costs to write the protocols, obtain clearance from all governing bodies, prepare the study site for the study, implement the study, analyze the data, and disseminate the data at local and international fora, and publish manuscripts over a four-year period.

Personnel: This includes the entomological and epidemiological staff who will be performing the field monitoring of the cohort, continuous household survey, outpatient health facility surveillance, ATSB monitoring and entomological monitoring. Additionally, it includes the salaries for study coordinators and support staff, such as administrators and drivers.

Supplies: This includes the costs of the RDTs, filter papers, LLINs, antimalarials, laboratory reagents for PCR, software licenses, and airtime.

Equipment: This includes a freezer for the storage of samples.

Other Direct Costs: This includes the costs of tablets and laptops for data collection, the costs of local travel to the communities, including motorbike and transport fees, ethical review processing, sponsorship governance, and CME training.

Travel: This includes international travel fees for the Entomology co-PI to attend international conferences in each of the years of the study and travel for consultants from the USA and UK to provide technical expertise to the study. It also includes domestic travel to present to the Kenya Ministry of Health (National Malaria Control Program) in Nairobi.

Indirect costs: These include the indirect costs necessary for operating on the KEMRI-CGHR platform and for support to the LSTM offices in the UK.

15 REFERENCES

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16 ANNEXES

16.1 ANNEX I. DINOTEFURAN SAFETY DATA SHEET

SAFETY DATA SHEET

Date: 13, July, 2015
Serial No.: AGH10007Ec_03

SECTION 1: IDENTIFICATION OF THE SUBSTANCE AND OF THE COMPANY
1.1. PRODUCT IDENTIFIER

Product Name **Dinotefuran Technical**

IUPAC NAME: (*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine
CAS NAME: *N*-methyl-*N'*-nitro-*N''*-((tetrahydro-3-furyl)methyl)guanidine
CAS No.: 165252-70-0, EC No.: 605-399-0, CIPAC No: 749

1.2. RELEVANT IDENTIFIED USES OF THE SUBSTANCE AND USES ADVISED AGAINST
Use of Product Active ingredient of insecticide

1.3. DETAILS OF THE SUPPLIER OF THE SAFETY DATA SHEET
Manufacturer/Supplier of the Product
Mitsui Chemicals Agro, Inc.
Nihonbashi Dia Building, 1-19-1, Nihonbashi, Chuo-ku, Tokyo
103-0027, JAPAN
Telephone: +81-3-5290-2810
Telefax: +81-3-3231-1183
e-mail: mcag-msds@mitsui-chem.co.jp

1.4. EMERGENCY TELEPHONE NUMBER
Mitsui Chemicals Agro, Inc. +81-3-5290-2810 (office hour only; Japan standard time: JST)

SECTION 2: HAZARDS IDENTIFICATION
2.1. CLASSIFICATION OF THE SUBSTANCE
Classification according to Regulation (EC) No 1272/2008
Aquatic Acute 1: H400 (M=10)
Aquatic Chronic 1: H410 (M=10)

2.2. LABEL ELEMENTS
Label Elements according to Regulation (EC) No 1272/2008
Hazard Pictograms

Signal Word Warning

Hazard Statements
H410: Very Toxic to aquatic life with long lasting effects.

Precautionary Statements
Prevention
P273: Avoid release to the environment.

Response
P391: Collect spillage.

Disposal

P501: Dispose of contents or container in accordance with local, regional, national or international regulations.

2.3. OTHER HAZARDS

Toxic to bees.
Dinotefuran is self-reactive under high temperatures.
Exposure to heat may promote violent decomposition.

SECTION 3: COMPOSITION/INFORMATION ON INGREDIENTS

Common Name: Dinotefuran
Purity: ≥99.1%
IUPAC Name: (*RS*)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine
CAS No.: 165252-70-0, EC No.: 605-399-0, CIPAC No: 749

SECTION 4: FIRST AID MEASURES

4.1. DESCRIPTION OF FIRST AID MEASURES

Ingestion

Rinse mouth with water. Get medical attention immediately. Induce vomiting as directed by medical personnel. Never give anything by mouth to an unconscious or convulsing person.

Inhalation

If you feel unwell, move to fresh air immediately. Get medical attention if cough or other symptoms develop. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.

Skin Contact

Immediately remove contaminated clothing and shoes. Flush skin and clean off with large amounts of water. Get medical attention if symptoms develop.

Eye Contact

Immediately flush with plenty of water. Part eyelids with fingers to assure complete flushing. Check for and remove contact lenses if easily possible. Get medical attention if irritation persists.

SECTION 5: FIREFIGHTING MEASURES

5.1. EXTINGUISHING MEDIA

Suitable Extinguishing Media

Foam, water

Unsuitable Extinguishing Media

CO_2 or dry chemical are not effective for extinguish.

5.2. SPECIAL HAZARDS ARISING FROM THE SUBSTANCE

General Hazard

Emits toxic fumes in fire condition.
This product is not expected to burn or explode in normal conditions, but will burn violently if involved in fire. Dinotefuran is self-reactive under high temperatures. Exposure to heat may promote violent decomposition.

Hazardous Combustion Products

Nitrogen oxides.

5.3. ADVICE FOR FIREFIGHTERS

Firefighting Instructions

Keep unnecessary and unprotected personnel away. Shut off supply if possible. Remove

containers to safe place if possible. Keep containers and surroundings cool by spraying with water. Fight fire from an upwind position.

Firefighting Equipment

Respiratory and eye protection is required for firefighting personnel.
Full protective equipment and self-contained breathing apparatus (SCBA) should be used for all indoor fires and any significant outdoor fires.

SECTION 6: ACCIDENTAL RELEASE MEASURES

6.1. PERSONAL PRECAUTIONS, PROTECTIVE EQUIPMENT AND EMERGENCY PROCEDURES

Warn and evacuate in the neighborhood as necessary. Keep unnecessary and unprotected personnel away. Wear appropriate personal protective equipment as specified in Section 8. Remove all sources of ignition. Stop leak if possible without personal risk.

6.2. ENVIRONMENTAL PRECAUTIONS

Do not let this product enter the environment.

6.3. METHODS AND MATERIAL FOR CONTAINMENT AND CLEANING UP

Use non-sparking tools and equipment.
Scoop or sweep up the spilled product and place it in a disposal container.
Use appropriate tools. Avoid dispersal of dust in the air.

SECTION 7: HANDLING AND STORAGE

7.1. PRECAUTIONS FOR SAFE HANDLING

Technical Measures

Use only with adequate ventilation.
Where there may be potential of fire or explosion hazard, use explosion-proof electrical equipment and take precautions against build-up of electrostatic charges.
Wear appropriate personal protective equipment. Keep away from heat, sparks, open flames and hot surfaces.

Precautions

Handle with care. Do not breathe dust. Avoid contact with eyes, skin and clothing.
Take precautionary measures against static discharge.

Advice on general occupational hygiene

Provide hand and eye wash station near work area. Wash hands thoroughly after use. Take off contaminated protective equipment before entering rest areas. Do not eat, drink or smoke when using this product.

7.2. CONDITIONS FOR SAFE STORAGE, INCLUDING ANY INCOMPATIBILITIES

Storage Conditions

Keep away from heat, flame, all sources of ignition, and combustible material. Store in a cool, dark and well ventilated area. Keep container tightly closed and sealed until ready for use.
Do not contaminate other pesticides, fertilizers, water, foodstuffs or feed by storage and disposal.

Packaging Materials

Metal drum or conductive container.

7.3. SPECIFIC END USES

Biocide products subject to Regulation (EU) No 528/2012

SECTION 8: EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1. CONTROL PARAMETERS

Occupational Exposure Limit Values

Not established for this substance

8.2. EXPOSURE CONTROLS

Appropriate Engineering Controls

Provide general ventilation. Using closed system or local exhaust ventilation is recommended.
Provide safety shower and eye wash station near work area.

Personal Protection

Eye/face protection:	Safety glasses, goggles.
Skin Protection:	
Hand protection:	Chemical resistant gloves.
Body Protection:	Safety helmet, protective clothing, safety boots.
Respiratory protection:	Dust respirator

SECTION 9: PHYSICAL AND CHEMICAL PROPERTIES

Appearance:	White crystalline powder.
Odour:	None.
pH (1%, 25°C):	5.6
Melting point:	107.5°C
Initial boiling point and boiling range:	Not applicable (decomposes)
Flash point:	Not available
Auto-ignition temperature:	350°C
Upper/lower flammability or explosive limits	
Minimum explosive concentration:	45 mg/L
Limiting oxygen concentration:	11%
Minimum ignition energy:	81 mJ
Vapour pressure(30°C):	$<1.7\times10^{-6}$ Pa
Density (20°C):	1.40 g/mL
Solubilities (20°C):	40 g/L in water 57 g/L in methanol 9.0×10^{-6} g/L in hexane
Partition coefficient n-octanol/water (25°C):	Log Pow -0.549
Exothermic onset temperature:	217°C 111.5°C (by ARC test)

SECTION 10: STABILITY AND REACTIVITY

10.1. REACTIVITY

Risk of dust explosion.

10.2. CHEMICAL STABILITY

Stable under normal conditions.

10.3. POSSIBILITY OF HAZARDOUS REACTIONS

Dinotefuran is self-reactive under high temperatures.
Exposure to heat may promote violent decomposition.

10.4. CONDITIONS TO AVOID

Exposure to heat, ignition sources.

10.5. INCOMPATIBLE MATERIALS

Strong oxidizing agents

10.6. HAZARDOUS DECOMPOSITION PRODUCTS

Nitrogen oxides.

SECTION 11: TOXICOLOGICAL INFORMATION

Acute Toxicity

Oral:	Rat	LD_{50} 2450 mg/kg	[Not classified]
Dermal:	Rat	LD_{50} >2000 mg/kg	[Not classified]
Inhalation:	Rat	LC_{50} >4.09 mg/L/4hr	[Classification not possible]

Skin Corrosion/Irritation

Rabbit	Mild Irritant	[Not classified]

Serious Eye Damage/Irritation

Rabbit	Mild irritant	[Not classified]

Respiratory Sensitization	Not available	[Classification not possible]

Skin Sensitization

Guinea pig	Not a skin sensitizer.	[Not classified]

Germ Cell Mutagenicity

in vitro test		
Ames test :	Negative	
Chromosomal aberration:	Negative	
in vivo test		
Micronucleus test :	Negative	[Not classified]

Carcinogenicity

Rat, Mouse	Non-carcinogen.	[Not classified]

Reproductive Toxicity

Rat, Rabbit	No reproductive toxicity	[Not classified]

Specific Target Organ Toxicity

Single Exposure:	Not available	[Classification not possible]
Repeated Exposure:	Not available	[Classification not possible]

Aspiration Hazard	Not available	[Classification not possible]

SECTION 12: ECOLOGICAL INFORMATION

Hazardous to the Aquatic Environment (Acute)

Classified as category 1 based on the LC_{50} for chironomid. [Category 1 (M=10)]

Hazardous to the Aquatic Environment (Chronic)

Classified as category 1 based on the NOEC for chironomid and lack of rapid degradability. [Category 1 (M=10)]

12.1. TOXICITY

Carp	LC_{50} (96hr)	>100 mg/L
Daphnia magna	EC_{50} (48hr)	>1000 mg/L
Saltwater mysid		
Mysidopsis bahia	LC_{50} (96hr)	0.79 mg/L
Americamysis bahia	NOEC	0.089 mg/L

Chironomid (*Chironomus riparius*, water spiked study)

LC_{50} (48hr)	0.0721 mg/L
NOEC (27d)	0.00288 mg/L

Algae (*Pseudokirchneriella subcapitata*)
ErC_{50} (0-72hr) >100 mg/L

Dinotefuran is toxic to silk worm and bees.

12.2. PERSISTENCE AND DEGRADABILITY

Biodegradation: Not readily biodegradable.
Hydrolytic Half-Life: 1 year or more (at 25°C, pH 4, 7, 9)
Photolytic Half-Life: 3.8hr (at 25°C, 400 W/m^2, 300-800 nm)

12.3. BIOACCUMULATIVE POTENTIAL

Unlikely

12.4. MOBILITY IN SOIL

Not available.

SECTION 13: DISPOSAL CONSIDERATIONS

13.1. WASTE TREATMENT METHODS

Waste from Residues

Waste must be disposed of in accordance with federal, state, local, national and international regulations.

Contaminated Packaging

Empty the container completely before disposal.

SECTION 14: TRANSPORT INFORMATION

14.1. UN NUMBER

UN3077

14.2. UN PROPER SHIPPING NAME

ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (Dinotefuran)

14.3. TRANSPORT HAZARD CLASS

9

14.4. PACKING GROUP

III

14.5. ENVIROMENTAL HAZARDS

Marine pollutant

14.6. SPECIAL PRECAUTIONS FOR USER

Special Precautions for Transport

Make sure that the containers have no puncture or leakage. Avoid rough handling and dropping. Prevent collapse of cargo piles.

SECTION 15: REGULATORY INFORMATION

15.1. SAFETY, HEALTH AND ENVIRONMENTAL REGULATIONS/LEGISLATION SPECIFIC FOR THE SUBSTANCE

EU Status

Dinotefuran is listed in the European Chemicals Agency's pre-registered substances list (EC No. 605-399-0). Dinotefuran is intended for use as Product Type 18 and is a candidate for substitution under Regulation (EU) No. 528/2012.

Responsibility for compliance with applicable laws and regulations is with the user.

SECTION 16: OTHER INFORMATION

References

In-house data

Classification System

Classification according to Regulation (EC) No 1272/2008 of the European Parliament an the Council of 16 December 2008 on classification, labeling and packaging of substances mixtures, amending Regulation (EC) No 1907/2006.

Significant change from previous version

SECTION 2 Delete Classification according to Directive 67/548/EEC
SECTION 11 Acute toxicity Dermal test animal

To the best of our knowledge, the information contained herein is accurate.
However, we cannot assume any liability whatsoever for the accuracy or completeness of information contained herein.
Final determination of suitability of any material is the sole responsibility of the user. All mate may present unknown hazards and should be used with caution. Although certain hazards described herein, we cannot guarantee that these are the only hazards that exist.

16.2 ANNEX II: DENATONIUM BENZOATE SAFETY DATA SHEET

SIGMA-ALDRICH sigma-aldrich.com

SAFETY DATA SHEET

Version 5.4
Revision Date 12/15/2016
Print Date 11/10/2018

1. PRODUCT AND COMPANY IDENTIFICATION

1.1 Product identifiers

Product name : Denatonium benzoate

Product Number : D5765
Brand : Aldrich

CAS-No. : 3734-33-6

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Laboratory chemicals, Synthesis of substances

1.3 Details of the supplier of the safety data sheet

Company : Sigma-Aldrich
3050 Spruce Street
SAINT LOUIS MO 63103
USA

Telephone : +1 800-325-5832
Fax : +1 800-325-5052

1.4 Emergency telephone number

Emergency Phone # : +1-703-527-3887 (CHEMTREC)

2. HAZARDS IDENTIFICATION

2.1 Classification of the substance or mixture

GHS Classification in accordance with 29 CFR 1910 (OSHA HCS)
Acute toxicity, Oral (Category 4), H302
Chronic aquatic toxicity (Category 4), H413

For the full text of the H-Statements mentioned in this Section, see Section 16.

2.2 GHS Label elements, including precautionary statements

Pictogram

Signal word Warning

Hazard statement(s)
H302 Harmful if swallowed.
H413 May cause long lasting harmful effects to aquatic life.

Precautionary statement(s)
P264 Wash skin thoroughly after handling.
P270 Do not eat, drink or smoke when using this product.
P273 Avoid release to the environment.
P301 + P312 + P330 IF SWALLOWED: Call a POISON CENTER/doctor if you feel unwell. Rinse mouth.
P501 Dispose of contents/ container to an approved waste disposal plant.

2.3 Hazards not otherwise classified (HNOC) or not covered by GHS - none

3. COMPOSITION/INFORMATION ON INGREDIENTS

3.1 Substances

Synonyms : *N,N*-Diethyl-*N*-[(2,6-dimethylphenylcarbamoyl)methyl]benzylammonium benzoate
Benzyldiethyl(2,6-xylylcarbamoylmethyl)ammonium benzoate

Formula : $C_{28}H_{34}N_2O_3$
Molecular weight : 446.58 g/mol
CAS-No. : 3734-33-6
EC-No. : 223-095-2

Hazardous components

Component	Classification	Concentration
Denatonium benzoate		
	Acute Tox. 4; Aquatic Chronic 4; H302, H413	<= 100 %

For the full text of the H-Statements mentioned in this Section, see Section 16.

4. FIRST AID MEASURES

4.1 Description of first aid measures

General advice
Consult a physician. Show this safety data sheet to the doctor in attendance.Move out of dangerous area.

If inhaled
If breathed in, move person into fresh air. If not breathing, give artificial respiration. Consult a physician.

In case of skin contact
Wash off with soap and plenty of water. Consult a physician.

In case of eye contact
Flush eyes with water as a precaution.

If swallowed
Never give anything by mouth to an unconscious person. Rinse mouth with water. Consult a physician.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
No data available

5. FIREFIGHTING MEASURES

5.1 Extinguishing media

Suitable extinguishing media
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

5.2 Special hazards arising from the substance or mixture
No data available

5.3 Advice for firefighters
Wear self-contained breathing apparatus for firefighting if necessary.

5.4 Further information
No data available

6. ACCIDENTAL RELEASE MEASURES

6.1 Personal precautions, protective equipment and emergency procedures
Use personal protective equipment. Avoid dust formation. Avoid breathing vapours, mist or gas. Ensure adequate ventilation. Avoid breathing dust.

If used in solution, or mixed with other substances, and under conditions which differ from EN 374, contact the supplier of the CE approved gloves. This recommendation is advisory only and must be evaluated by an industrial hygienist and safety officer familiar with the specific situation of anticipated use by our customers. It should not be construed as offering an approval for any specific use scenario.

Body Protection
Complete suit protecting against chemicals, The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

Respiratory protection
For nuisance exposures use type P95 (US) or type P1 (EU EN 143) particle respirator.For higher level protection use type OV/AG/P99 (US) or type ABEK-P2 (EU EN 143) respirator cartridges. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Control of environmental exposure
Prevent further leakage or spillage if safe to do so. Do not let product enter drains. Discharge into the environment must be avoided.

9. PHYSICAL AND CHEMICAL PROPERTIES

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: crystalline Colour: white
b)	Odour	No data available
c)	Odour Threshold	No data available
d)	pH	No data available
e)	Melting point/freezing point	Melting point/range: 164 - 168 °C (327 - 334 °F) - lit.
f)	Initial boiling point and boiling range	No data available
g)	Flash point	100 °C (212 °F) - ISO 2719
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	No data available
j)	Upper/lower flammability or explosive limits	No data available
k)	Vapour pressure	No data available
l)	Vapour density	No data available
m)	Relative density	0.3846 g/cm3 at 26 °C (79 °F)
n)	Water solubility	42.55 g/l at 25 °C (77 °F) - completely soluble
o)	Partition coefficient: n-octanol/water	log Pow: 2.205 at 25 °C (77 °F)
p)	Auto-ignition temperature	No data available
q)	Decomposition temperature	No data available
r)	Viscosity	No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	No data available

9.2 Other safety information
No data available

10. STABILITY AND REACTIVITY

10.1 Reactivity
No data available

10.2 Chemical stability
Stable under recommended storage conditions.

10.3 Possibility of hazardous reactions
No data available

10.4 Conditions to avoid
Avoid moisture.

10.5 Incompatible materials
Strong oxidizing agents

10.6 Hazardous decomposition products
Hazardous decomposition products formed under fire conditions. - Carbon oxides, Nitrogen oxides (NOx)
Other decomposition products - No data available
In the event of fire: see section 5

11. TOXICOLOGICAL INFORMATION

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - 584 mg/kg
Remarks: Behavioral:Somnolence (general depressed activity). Behavioral:Tremor. Behavioral:Ataxia.

LC50 Inhalation - Rat - male and female - 4 h - > 8.7 mg/l
(OECD Test Guideline 403)

LD50 Dermal - Rat - male and female - > 2,000 mg/kg
(OECD Test Guideline 402)

No data available

Skin corrosion/irritation
No data available

Serious eye damage/eye irritation
Eyes - Rabbit
Result: No eye irritation
(OECD Test Guideline 405)

Respiratory or skin sensitisation
Germ cell mutagenicity
No data available

gene mutation test
Result: negative

Carcinogenicity

IARC: No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

NTP: No component of this product present at levels greater than or equal to 0.1% is identified as a known or anticipated carcinogen by NTP.

OSHA: No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by OSHA.

Reproductive toxicity
No data available

No data available

Specific target organ toxicity - single exposure

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

Additional Information
RTECS: BO6650000

To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

12. ECOLOGICAL INFORMATION

12.1 Toxicity

Toxicity to fish	LC50 - Danio rerio (zebra fish) - > 100 mg/l - 96 h (OECD Test Guideline 203)
Toxicity to algae	EC50 - Chlorella vulgaris (Fresh water algae) - 281.556 mg/l - 72 h (OECD Test Guideline 201)

12.2 Persistence and degradability

Biodegradability	aerobic - Exposure time 28 d Result: 18.17 % - According to the results of tests of biodegradability this product is not readily biodegradable. (OECD Test Guideline 301F)

12.3 Bioaccumulative potential

12.4 Mobility in soil

12.5 Results of PBT and vPvB assessment
PBT/vPvB assessment not available as chemical safety assessment not required/not conducted

12.6 Other adverse effects
An environmental hazard cannot be excluded in the event of unprofessional handling or disposal.

No data available

13. DISPOSAL CONSIDERATIONS

13.1 Waste treatment methods

Product
Offer surplus and non-recyclable solutions to a licensed disposal company.

Contaminated packaging
Dispose of as unused product.

14. TRANSPORT INFORMATION

DOT (US)
Not dangerous goods

IMDG
Not dangerous goods

IATA
Not dangerous goods

15. REGULATORY INFORMATION

SARA 302 Components
No chemicals in this material are subject to the reporting requirements of SARA Title III, Section 302.

SARA 313 Components

16.3 ANNEX III: ATSB STATIONS: DISPOSAL OPTIONS ASSESSMENT

IVCC

ATSB (attractive toxic sugar bait) stations: Disposal Options Assessment

31 July 2018

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Working Draft Report – For Client Review and Comment

For and on behalf of Environmental Resources Management Limited
Approved by:
Signed:
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EXECUTIVE SUMMARY

ERM was commissioned to undertake a high level review of disposal options for spent ATSB feeding stations (mosquito bait stations).

There are environmental and human health concerns associated with the potential disposal of the spent bait stations mainly related to the presence of the insecticide dinotefuran. Dinotefuran is a neonicotinoid i.e. it is highly toxic to non-target insects such as bees. It is also toxic to aquatic organisms and persistent in the water environment. There are possible unacceptable health risks to children if there is a likelihood of overexposure.

The options for managing the waste bait stations were initially considered in the context of waste hierarchy. It is likely that, given the nature of the waste, disposal (as opposed to recycling or recovery) is the most viable option with the key criteria for the disposal being:

- No direct or indirect discharge to water courses and/or groundwater
- No direct access for bees or plant uptake & indirect access by bees
- No direct access for children

The main disposal options available are likely to be burial either locally or in a municipal or equivalent site; or incineration either in a health care waste (HCW) facility or locally. Additional information from the manufacturer relating to composition and incineration, would be useful. It is likely that the waste bait stations are suitable for relatively high temperature combustion, although compliance with air emission and moisture content limits would need to be established.

This high level assessment was based on review of the three trial countries – Kenya, Mali & Zambia. Disposal options may vary for other countries such that some options not considered viable here (e.g. waste to energy) may be viable options for future wide deployment of the product.

The selection of any of these options may be constrained by the regulatory regime (waste & pesticides), handling and disposal, logistics (storage and transport) and feasibility (availability of facilities, acceptance criteria). It is possible that the bait stations could be classified as hazardous waste. These constraints will need to be considered in detail for each country. The target communities selected should be contacted to provide information on existing waste management processes, particularly the proximity of waste facilities of local hospitals / health clinics and transport links.

The feasibility of collecting the spent bait stations during the redeployment of the new bait stations is considered to be viable, and may enable inclusion of more distant but suitable facilities for disposal. It is assumed if required that the spent bait stations could be temporarily stored in a secure drum before being collected en masse.

A first-pass multi-criteria analysis (MCA) was undertaken of the main disposal options using an in-house ERM tool. The options assessed were:

- burial in a municipal or equivalent site;
- local burial;
- incineration in HCW facility; and
- local incineration.

The MCA tool is a subjective but useful screening tool that allows structural comparison by weighting and then scoring the positive and negative environmental, social (including health) and economic impacts of the different options. The MCA showed that all options had overall negative environmental impacts but in the case of HCW incineration (and to a lesser extent local incineration) these were outweighed by the combined social and economic criteria. This is largely due to the predicted tangible benefits of the programme objectives compared to the more hypothetical adverse environmental impacts.

For some communities there may be an obvious preferred suitable and controlled disposal option. However where that is not the case, MCA could be undertaken as a useful means of comparing options and to inform the decision-making process and it could be extended to include input / engagement with stakeholders if this is considered feasible and subject to an understanding of exposure and risk.

Overall, it is concluded that HCW is the preferred option where feasible. Local burial raised the most human health and environmental concerns. However, the information provided in this report, together with use of the MCA tool as required, may facilitate an informed risk management decision at the local level on the most appropriate disposal option.

CONTENTS

CONTENTS

1 INTRODUCTION

1.1 COMMISSION

Environmental Resources Management (ERM) was commissioned by the IVCC (Innovative Vector Control Consortium) to review disposal options for ATSB (attractive toxic sugar bait) feeding stations – also known as mosquito bait stations – following use. The intention is to use the bait stations in homes in rural areas in malarial zones of countries in Africa/Asia with trials initially in Mali, Kenya and Zambia.

ERM (JSC) had earlier undertaken a preliminary assessment of the risks to human health and the environment [1] from the bait stations as in use. Following this, ERM was approached to consider the risks from burying the bait stations locally but this was viewed to be reasonably high risk (this option is discussed later), and ERM recommended that a high level review of other disposal options was undertaken.

The layout of this report is as follows:

- *Section 1* – Introduction;
- *Section 2* – Waste Hierarchy;
- *Section 3* – Disposal Options Assessment; and
- *Section 4* – Conclusions and Recommendations.

1.2 BAIT STATIONS

The ATSB feeding stations comprise a polyester/polyethene laminate and film membrane bag containing 100g of sucrose solution with 0.1% (0.1g i.e. 100mg) of dinotefuran, an insecticide. The mosquito's proboscis punctures the membrane to allow ingestion of the treated sugar with the membrane rapidly re-sealing following withdrawal to prevent the sugar solution leaking. A photograph of the bait station is shown in *Figure 1.2a*. (*What is the composition of the film membrane if different from the polyester / polyethene laminate? It may have consequences for disposal*).

The bait stations are placed around the home (out of reach of young children) and replaced every 6 months. The latter is based on the anticipated lifespan of the bait station rather than significant reduction or degradation of the dinotefuran content. The concentration of dinotefuran after 6 months is expected to be comparable to the initial concentration. The number of bait stations/households in any location will vary dependent on the size of the community. It has been assumed that a reasonable maximum is 1,000 bait stations per community.

(1) Overview of human health and environmental risks of dinotefuran sugar bait feeders: Westham ATSB mosquito station, prepared by JSC International Ltd. for IVCC, 09 February 2017.

Figure 1.2a ATSB Feeding Station (scale not known)

1.3 DINOTEFURAN

Information on dinotefuran has largely been drawn from the EU European Chemicals Agency (ECHA) and US Environmental Protection Agency (USEPA) evaluation reports [1] [2] and summarised briefly below. The documents should be referenced for specific details.

- Composition: $C_7H_{14}N_4O_3$, CAS No. 165252-70-0, 1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl) guanidine;
- Neonicotinoid insecticide - a systemic agricultural, neuro-active insecticide i.e. it is transported through plants if uptake, and will harm non-target arthropods such as bees;
- Non-volatile, non-flammable, crystalline solid with melting point of c. 108°C; decomposing at c. 208°C;
- Readily soluble in water – solubility 54,300mg/l @ 20°C [3];
- Considered to have high mobility in soil and strong potential to leach;

(1) European Chemicals Agency: Regulation (EU) No. 528/2012 concerning the making available on the market and use of biocidal products: Evaluation of active substances: Assessment Report: Dinotefuran, Product-type 18 (insecticides, acaricides and to control other arthropods), 17 June 2014, UK.
(2) United States Environmental Protection Agency (USEPA): Office of Prevention, Pesticides and Toxic Substances: Pesticide Fact Sheet: Dinotefuran, Conditional Registration, September 2004.
(3) Tomlin CDS, ed. Dinotefuran (165252-70-0). In: The e-Pesticide Manual, 13th Edition Version 3.1 (2004-05). Surrey UK, British Crop Protection Council (Source: TOXNET: Hazardous Substances Database).

- Degrades relatively rapidly in soil under aerobic conditions, more slowly under anaerobic conditions (main metabolites: MNG, DN and UF [1]). However it appears to degrade much more slowly in aquatic environments and there is little information on degradation in groundwater. Based on the (lack of) degradation (data) in the water environment it is considered persistent;
- Does not bio-accumulate;
- Human health: generally of low concern - low acute toxicity via ingestion, inhalation or dermal exposure. Causes low level skin irritation and moderate eye irritation. Not considered carcinogenic or mutagenic, no adverse reproductive toxicity, neurotoxicity or immunotoxicity;
- Exposure assessments undertaken for professional use (insecticide application to premises) with no PPE (personal protective equipment) and also for secondary exposure for adults (occupants of premises) estimated the risk to be acceptable - although dependent on exposure scenario there could be unacceptable risk to children (addressed for proposed use by earlier ERM (JSC) assessment); and
- Water environment: toxic to aquatic life

Key points for waste management:

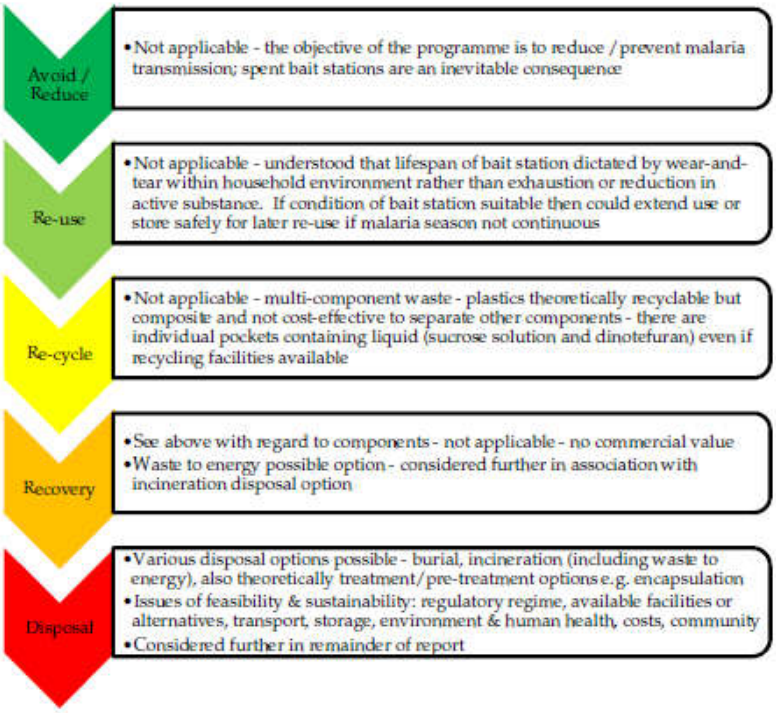
- No direct or indirect discharge to water courses and/or groundwater
- No direct access for bees or plant uptake & indirect access by bees
- No direct access for children

The other components of the bait stations do have some bearing on the disposal options but are less critical than the pesticide content – and are discussed later as relevant to the specific options.

(1) MNG: 1 methyl-2-nitroguanidine; DN: 1-methyl-3-(tetrahydro-3-furylmethyl) guanidinium; and UF: M1; 1-methyl-3-(tetrahydro-3-furylmethyl) urea. The metabolites have not been considered further in this review.

2 WASTE HIERARCHY

A waste hierarchy sets out a sequence of options for managing waste. The different options (in order of preference) have been considered below:



Disposal is the most appropriate form of waste management for the spent bait stations based on their current design and materials employed.

3 DISPOSAL OPTIONS ASSESSMENT

3.1 REGULATORY CONTEXT

All three countries (Kenya, Mali and Zambia) selected for the trial have regulatory guidance covering waste management and the environment, as well as regulation of the registration of pesticides, use and transport. This will be the case for most jurisdictions. Specifics vary and there may be exemptions due to nature of programme (both as trial and health/welfare benefits) but the following points may require consideration:

- Prevention of discharge or disposal of wastes in such a manner that will cause pollution of the environment or adverse impact on human health;
- Prohibition of discharge or disposal of hazardous waste without regulatory authorisation and controls;
- The toxic and persistent nature of the pesticide may cause the waste to be classified as hazardous;
- Potential exemption if classified as domestic waste as generated by individual households but issues over controlled storage, collection and transportation (i.e. waste carrier);
- Requirement that pesticide is registered, controls over transportation; and
- Charges associated with some regulatory compliance.

Dinotefuran is registered for use in Kenya as the active substance in the insecticide 'Starkle 20 SG'. It has not been possible to find recent registration lists for Mali or Zambia.

3.2 LOGISTICS

As discussed below, available existing facilities for disposal are largely distant from the rural communities where the mosquito bait stations will be used and the connecting infrastructure is frequently poor. However, following the initial supply, the bait stations will need to be replaced periodically, thus there is an opportunity to align the delivery of replacement bait stations with the collection of spent bait stations. This may require temporary secure / controlled storage facilities (drums or covered skip could be suitable).

3.3 EXISTING WASTE MANAGEMENT

Details on existing waste management arrangements for rural areas are limited and will be variable. During the review process, it became apparent that extensive consideration had been given to strategic planning for health-

care waste management within the countries [1] [2] [3]as well as non-country specific publications by international bodies such as the World Health Organisation and the International Committee of the Red Cross. There are some clear parallels with this commission (potentially hazardous waste, plastics), as well as some significant differences. These documents provide much useful information.

There may be local burial pits, some secure others open and unlikely to contain any engineered liner; waste is often burned either in skips, open fires or less frequently incinerators (if present - usually located at health-care facilities). Private collectors operate in some areas. Generally, waste management does not appear well controlled but left to individuals or the local community.

3.4 BURIAL

3.4.1 *Existing Controlled Waste /Landfill Facilities*

While the details differ between countries, the number of existing controlled waste facilities (or dump sites as more commonly referenced) in any of these countries is limited. These facilities are located in the larger conurbations and there is a mixture of government and commercial operation varying between countries. These municipal facilities appear to be largely if not all at capacity although there are plans for extensions, new facilities, recycling and recovery dependent on funding. The capacity for receiving hazardous waste varies between limited and non-existent. It is not known whether the sites are engineered – lined, leachate /emissions collection - or to what extent waste management is controlled through segregation, cover etc. As it is widely reported that communities both live and work on the waste sites – scavenging the waste for materials to sell or re-use – there appears little control. In the longer term, there may be suitable facilities available, but the existing facilities appear unsuitable. There is therefore potential impact on the environment and human health from the spent bait stations at the facilities as well as the sparsity of facilities, little or no capacity and distance with respect to the rural areas. If the collection of the spent bait stations can be co-ordinated with the delivery of the replacement bait stations, the distance from suitable facilities may not be such a concern.

3.4.2 *Local Burial*

If local lined secure pits with controlled disposal are available and the spent bait stations acceptable, these locations could be suitable. Otherwise, there are potential concerns with this approach:

(1) Ministry of Health, Republic of Kenya, Health Care Waste Management Plan 2016-2021
(2) Ministry of Health, Republic of Zambia, National Health-Care Waste Management Plan 2015 - 2019
(3) Republique Du Mali, Ministere De La Santé & Banque Mondiale, Actualisation Du Plan De Gestion Des Déchets Biomédicaux, Draft, Juin 2011, Ref. E2867 (this appears to be have been incorporated into an overlapping & ongoing World Bank Western Africa initiative REDISSE (Regional Disease Surveillance Systems Enhancement) which includes waste management)

- Open pit - access to the waste by children (or non-target arthropods/pollinating insects such as bees);
- Shallow burial;
  - Disturbance and access by children;
  - Plant growth and indirect access by pollinating insects by uptake of contaminated pollen and nectar (systemic activity);
  - Direct or indirect discharge to water environment;
- Deep burial (& below root zone);
  - Direct or indirect discharge to water environment; and
- Possible regulatory non-compliance.

Overall, local burial is unlikely to be suitable unless it is very well controlled. If necessary, site- specific risk assessment will be required to determine the potential environmental (and/or less likely human health) risks of local deposition of the spent mosquito bait stations (see discussion later).

3.5 INCINERATION

3.5.1 *Bait Station Suitability*

For the bait stations to be suitable for incineration, they need to be combustible and not to give rise to unsuitable/ non-compliant air emissions:

- Dinotefuran decomposes at c. 208°C and should breakdown to CO_2, H_2O, NO_x. Nitrogen oxides can be a significant source of air pollution (vehicle emissions, particularly diesel engines, are a major source). Despite it's name, dinotefuran is not a source of "furans" as polychlorinated dibenzofurans are commonly referred to. Furans (1) and dioxins are also significant air pollutants;
- The plastic laminate comprises polyethene, $(C_2H_4)_n$, and polyester (probably polyethene terephthalate (PET), $(C_{10}H_8O_4)_n$). Relatively high temperatures are required for combustion (polyethene melts at c. 80°C and PET at c. 260°C). There can be limits on plastics containing halogens e.g. PVC, thus the plastic component of the bait station should be suitable;
- There can be limits on moisture content of waste – which may be a problem as the bait stations contains liquid – the sucrose solution in which the dinotefuran is dissolved. Sucrose will combust at very high temperatures to form carbon (ash) and water (steam) otherwise more likely to decompose to form 'caramel'; and
- Residues will be generated – should be ashes – which need to be disposed of safely.

(1) A 'furan' is heterocyclic organic compound - an aromatic ring with four carbon atoms and one oxygen (dinotefuran contains such a ring). Substitution of the hydrogen atoms by chlorine or fluorine creates the "furans" that are of concern

If not done so previously, the manufacturers (Westham) should be contacted as they may have more product specific information.

Likely suitable for relatively high temperature combustion, although compliance with air emission and moisture content limits needs to be established.

3.5.2 *Municipal & other Incinerators*

Outside of health-care waste incinerators (discussed separately), there appear to be few incinerators for general domestic / commercial waste. There are various plans dependent on funding for waste to energy incinerators partly in association with re-working and recovery of existing dump sites as well as taking new waste streams, and as such will likely be located in the larger conurbations.

Other potential sources of incineration include industrial furnaces or kilns such as operated at cement plants and some metal processing plants. Such plants are not widely distributed although their location may be close to rural community. However, it is considered unlikely that these plants would be able to accept the waste – contains a toxic substance, potentially classified as hazardous as well as plastics – although the temperatures should be high enough to combust the waste and dinotefuran.

3.5.3 *Health Care Waste (HCW) Incinerators*

HCW is a significant concern for all of the three target countries, in part due to prevalence of infectious diseases such as HIV (human immunodeficiency virus), tuberculosis (TB) etc. A significant proportion of HCW is classified as hazardous including waste deemed toxic and/or chemical as well as many other categories. It also includes a significant proportion of associated plastic and liquid waste – bags, drips, syringes etc. Thus there are clear parallels with spent bait stations.

Due to the nature of HCW, particularly clinical/hazardous waste, there should be more controlled handling (appropriate PPE) and disposal – and indeed there is guidance available. The current preferred disposal option for the HCW is (high temperature) incineration. HCW incinerators are much more widely distributed, although this varies between countries, and are more likely to be nearby or at least closer to rural communities than other facilities discussed as they are located at hospitals and health clinics.

However as apparent from the strategic planning documents (see *Section 3.3*), HCW management does not consistently meet required standards. Not all facilities producing HCW have incinerators but a significant proportion do with recommendations in the strategic plans to procure and / or construct more. Not all incinerators are functioning, functioning properly or operated correctly. Many, possibly the majority, do not have measures to control air

emissions. There are many different incinerator types – double or single chamber – rotary kilns, brick-lined chambers etc. Double chambers can achieve higher temperatures.

The 'De Montford' medical incinerator is quite common – specifically designed for and widely used in Africa and Asia. It is double chambered and should reach high temperatures (>900°C). It is recognised that it is not the ideal solution from an environmental perspective (largely due to air emissions as well as burning of fuel and generation of greenhouse gases) but it is often the most viable option.

If incineration facilities are available with appropriate level of controls and the spent bait stations meet acceptance criteria, it is a viable disposal option.

This option requires liaison with the relevant HC facilities to include this waste stream and there may be charges. It is hoped that the facilities would be receptive to incorporating this waste stream, as the programme if successful will reduce malaria transmission and thus reduce the health care burden.

3.5.4 *Local Burning*

There may be local facilities in the form of fire pits, skips etc., which could be considered in the absence of more suitable incinerators discussed above – although there remain potential concerns if not controlled such that there is access by children and/or non-target arthropods. However, temperatures may not be high enough to burn the waste as required and there will be air emissions of potential health and environmental concern.

3.6 *Other Options*

Other options for HCW such as sterilisation, disinfection, microwave etc. are not suitable for the bait stations. Encapsulation is referenced in the HCW planning documents but does not appear to be used.

It is unlikely that pre-treatment is either available or suitable. Reducing the moisture content (some form of shredding / puncturing and drying?) would be beneficial but unlikely to be practicable or able to ensure that it is undertaken safely and securely.

3.7 *Multi-criteria Analysis and Sustainability*

A multi-criteria analysis (MCA) of the four main options has been undertaken. ERM has developed the MCA based on CL:AiRE SuRF-UK [1] indicators for environmental, social and economic categories. In each category there are a

(1) CL:AIRE SuRF-UK (Contaminated Land: Applications in Real Environments Sustainable Remediation Forum UK) Framework Annex 1: The SuRF-UK Indicator Set for Sustainable Remediation Assessment. 2011

number of criteria or 'indicators' e.g. in the environmental category there are criteria for water, soil, air, ecology and resources. The MCA aims to balance the various inputs by considering the overall net benefit or disbenefit of the three categories. The MCA is included in *Annex A* and summarised below.

The first stage is to undertake a weighting of the indicators (see *Figure 3.7a*) as they relate to the programme – what is important, what not so significant or influential, and then each option is graded according to magnitude of impact and duration, and given an overall score based on the impact that the option has on the indicators. While the scoring is largely negative or neutral (particularly for the environmental indicators) as dealing with different waste disposal options, it is possible to incorporate the overall health and welfare benefit of the ATSB feeding station programme within the social and some of the economic indicators.

Four options have been assessed:

- Option 1: Disposal of waste to distant (municipal) landfill or dumpsite;
- Option 2: Local burial of waste;
- Option3: Incineration of waste in a HCW incinerator; and
- Option 4: Local burning of waste.

The weighting and the scoring is subjective – particularly here as undertaken solely by the author of the report and also as the review of the options is not detailed but high level. The MCA included in *Annex A* is an example of the process. Ideally, representatives of the various people / groups / stakeholders (e.g. local communities, regulators, funders) involved in the programme should undertake the exercise with consensus reached on the weighting and the grading – this removes individual bias and more importantly allows what matters to the local communities to be properly considered and evaluated.

Weighting				
Least Important				Most Important
1	2	3	4	5

Impact Severity Matrix		DURATION				
		very short	short	medium	long	permanent
MAGNITUDE	none	0	0	0	0	0
	very little effect	0	0	0	0	1
	small	0	0	1	1	2
	moderate	0	1	2	3	3
	medium	1	2	3	4	4
	large	2	3	4	5	5
	very large effect	3	4	5	5	5

Figure 3.7a: Indicator Weighting (1 to 5) and Grading Scale (-5 to +5, depending on whether impact adverse or beneficial))

3.7.1 *MCA Results*

The weighting and grading of the three categories for the four options are shown below in *Table 3.7a* and *Figure 3.7b*. The results are a means to assist in

relative evaluation of the four options – however it is stressed again that it is subjective and based on high level review; an example of the MCA process. The weighting has not been applied evenly across the categories with social being allocated more significance than environmental and economic as it is assumed that the predicted social (and to lesser extent economic) benefits of the programme are tangible while the environmental disbenefits are largely potential / hypothetical. The specifics for any one community will differ dependent on what disposal facilities are actually available, how they are operated and the transport arrangements.

Table 3.7a *MCA*

Sustainability Indicator	Relative Weighting (1 – 5)	Grading (-5 - +5)			
		Option 1	Option 2	Option 3	Option 4
Environment					
Impact on water	3	-1	-3	0	-1
Impact on soil	1	-1	-1	0	0
Impact on air emissions – climate change & local	1	-1	0	-1	-2
Impact on ecology	3	-1	-3	0	-1
Natural resource use & waste generation	1	-2	-2	0	-1
Net Environmental Benefit (score range: ±45)		-10	-21	-1	-9
Social					
Human health chronic & acute risks	5	2	2	4	3
Ethics & equality	3	-1	1	0	0
Neighbourhood & locality	2	-1	-2	0	-1
Communities & community Involvement	3	0	1	0	1
Uncertainty & evidence	1	0	-1	0	-1
Net Social Benefit (score range: ±70)		5	11	20	15
Economic					
Direct economic costs & benefits	1	-3	-2	0	0
Indirect economic costs & benefits	4	1	0	2	1
Employment opportunities & human capital	1	0	1	0	0
Induced economic costs & benefits	2	0	-1	0	-1
Project lifespan & flexibility	0	0	0	0	0
Net Economic Benefit (score range: ±40)		1	-3	8	2
Net Benefit (score range: ±155)		-4	-13	27	8
Ranking		3	4	1	2

The results indicate that Option 3, disposal to a HCW incinerator (if available), is the most preferred option (highest positive net benefit score). None of the options have positive environmental benefits but Option 2 (local burial) has the worst score. This is based on potential risk. However if the location is far from surface water, groundwater is at depth and there are proper controls in terms of cover and depth of waste, then there would be significantly reduced impact and higher score. This method of disposal however would be difficult to regulate and control to ensure that the locations of burial were appropriate to minimise the risk. Unsurprisingly all options show a positive social score – reflecting the predicted health benefits, while economic criteria are largely

neutral but this is assuming a moderate level of compliance (i.e. no fines or legal costs) and relatively low scheme costs.

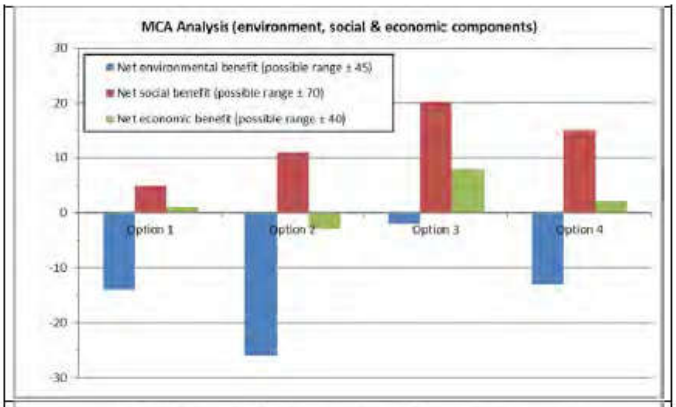


Figure 3.7b: Multi-Criteria Analysis

The discussion above shows that Option 3, disposal via HCW incineration is the preferred option. If Option 3 facilities are nearby and well-operated, this appears to be an obvious disposal arrangement option and further MCA consideration should not be required. Similarly, although less likely if Option 1, disposal to a managed landfill, is available and well–operated, this too is unlikely to require MCA. However, there will be situations where a suitable disposal route is not clear and this is where MCA could be of benefit on the decision-making process.

4 CONCLUSIONS AND RECOMMENDATIONS

There are environmental and human health concerns associated with the potential disposal of the spent bait station mainly related to the presence of the insecticide dinotefuran. Dinotefuran is toxic to aquatic organisms and persistent in the water environment. There are possible unacceptable health risks to children, largely from contact with the bait stations during or after poorly controlled disposal. It is also a neonicotinoid insecticide i.e. it is highly toxic to non-target insects such as bees and this class of chemistry is perceived very negatively by regulators and NGOs. Due to the systemic action of these pesticides, exposure to pollinators can result from uptake by plants and subsequent exposure to contaminated pollen.
Thus key criteria for management of the waste bait stations are:

- No direct or indirect discharge to water courses and/or groundwater
- No direct access for bees or plant uptake & indirect access by bees
- No direct access for children

It is likely that, given the nature of the waste, disposal (as opposed to recycling or recovery) is the most viable option. The main disposal options available are likely to be burial either locally or in a municipal or equivalent site; or incineration either in HCW facility or locally. The selection of any of these options may be constrained by the regulatory regime (waste & pesticides) handling and disposal, logistics (storage and transport) and feasibility (availability of facilities, acceptance criteria). It is possible that the bait stations could be classified as hazardous waste. These constraints will need to be considered in detail, particularly the regulatory regime and waste classification, for each country.

A first-pass multi-criteria analysis (MCA) was undertaken of the available options. The MCA is subjective but allows structural comparison of the positive and negative impacts of the different options. The MCA showed that all options had overall negative environmental impacts but in the case of HCW incineration (and to a lesser extent local incineration) these were outweighed by the combined social and economic criteria. This is largely due to the predicted tangible benefits of the programme objectives compared to the more hypothetical adverse environmental impacts.

The feasibility of collecting the spent bait stations during the redeployment of the new bait stations is considered to be viable, and may enable inclusion of more distant but suitable facilities for disposal. It is assumed if required that the spent bait stations could be temporarily stored in a secure drum before being collected en masse.

This high level assessment was based on review of the three trial countries – Kenya, Mali & Zambia. Disposal options may vary for other countries such that some options not considered viable here (e.g. waste to energy) may be viable options.

The manufacturer should be contacted to provide more information relating to composition and incineration.

The target communities if selected should be contacted to provide information on existing waste management processes, particularly the proximity of waste facilities of local hospitals / health clinics and transport links. For some communities there may be an obvious preferred suitable and controlled disposal option. However where that is not the case, MCA could be undertaken as a useful means of comparing options and to inform the decision-making process. It could be extended to include input / engagement with stakeholders if this is considered feasible; an understanding of exposure and risk is required. If considered helpful, ERM could facilitate this process with the IVCC. The MCA tool used here is quite a simple screening tool, and based on UK derived criteria. This is considered appropriate for this high level review. It could be adapted in consultation with IVCC to map criteria focussed on the country under consideration or alternatively, there are more sophisticated MCA models on which ERM could advise and assist.

Overall, it is concluded that HCW is the preferred option where feasible. Local burial raised the most human health and environmental concerns. However, the information provided in this report, together with use of the MCA tool as required, may facilitate an informed risk management decision at the local level on the most appropriate disposal option.

ANNEXES

Annex A

Example MCA

Sustainable Remediation Assessment: MCA Master based on CLARA Indicators

Multi Criteria/Attribute Analysis (MCA

Multi criteria analysis (MCA), sometimes called multi attribute analysis, is a decision aiding technique to help support decision makers faced with making numerous and sometimes conflicting evaluations.

Each remedial option is assessed using the same criteria.

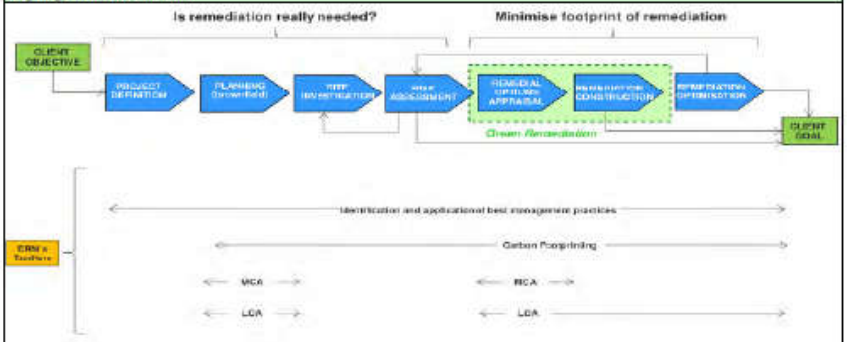
MCA aims to balance the various inputs by considering the overall net benefit of social, economic and environmental factors.

MCA and the Key Principles of Sustainable Remediation

Throughout the MCA process remember the principles of Sustainable Remediation:

1. *Protection of human health and the wider environment*
2. *Safe working practices*
3. *Consistent, clear and reproductive evidence based decision making*
4. *Record keeping and transparent reporting*
5. *Good governance and stakeholder involvement*
6. *Sound science*

Integrating Sustainable Remediation



A good understanding of the design of the remediation system is required so MCA fits better at the remedial options stage, it typically follows initial technical screening.

The MCA Tool

This MCA tool has been developed based upon the SuRF-UK indicator set for sustainable remediation. Project considerations are split into environment, social and economic categories, with various subcategories, as follows:

Environment
- *Groundwater & Surface water;*
- *Soil & Ground Conditions;*
- *Air;*
- *Ecology; and,*
- *Natural Resources & Waste.*

Social:
- *Human Health & Safety;*
- *Ethics & Equality;*
- *Neighbourhood & Locality;*
- *Communities & Community involvement; and,*
- *Uncertainty & Evidence (i.e. quality of investigations, robustness of decision making).*

Economic
- *Direct Economic Cost & Benefits;*
- *Indirect Economic Costs & benefits;*
- *Employment & Employment Capital;*
- *Induced Economic Costs & Benefits; and,*
- *Project Lifespan & Flexibility.*

Each of the categories is given a different weighting which will be determined on a project by project basis through discussion with the various stakeholders.
The output is a numerical value for environment, social and economic considerations making it easy to see which remedial option is most favourable from a sustainability focus.

Using the MCA Tool

The MCA tool contained herein allows you to assess up to four remediation alternatives plus the option of 'do nothing'.

Each of the relevant criterions (under the Social, Environment and Economic headings) is weighted and the various remedial alternatives are subsequently graded according to the selected criterion.

The weighting and grading exercises should ideally be done in discussion with the various stakeholders for the project. It is a great opportunity to get them involved!

First start with 'weighting' - In order to measure their relative importance, each relevant criterion under the Environment, Social and Economic set should be weighted on a scale of 1 to 5 where 5 would be most important and 1 would be least important. Adjustments to the weighting allow for a very flexible approach.

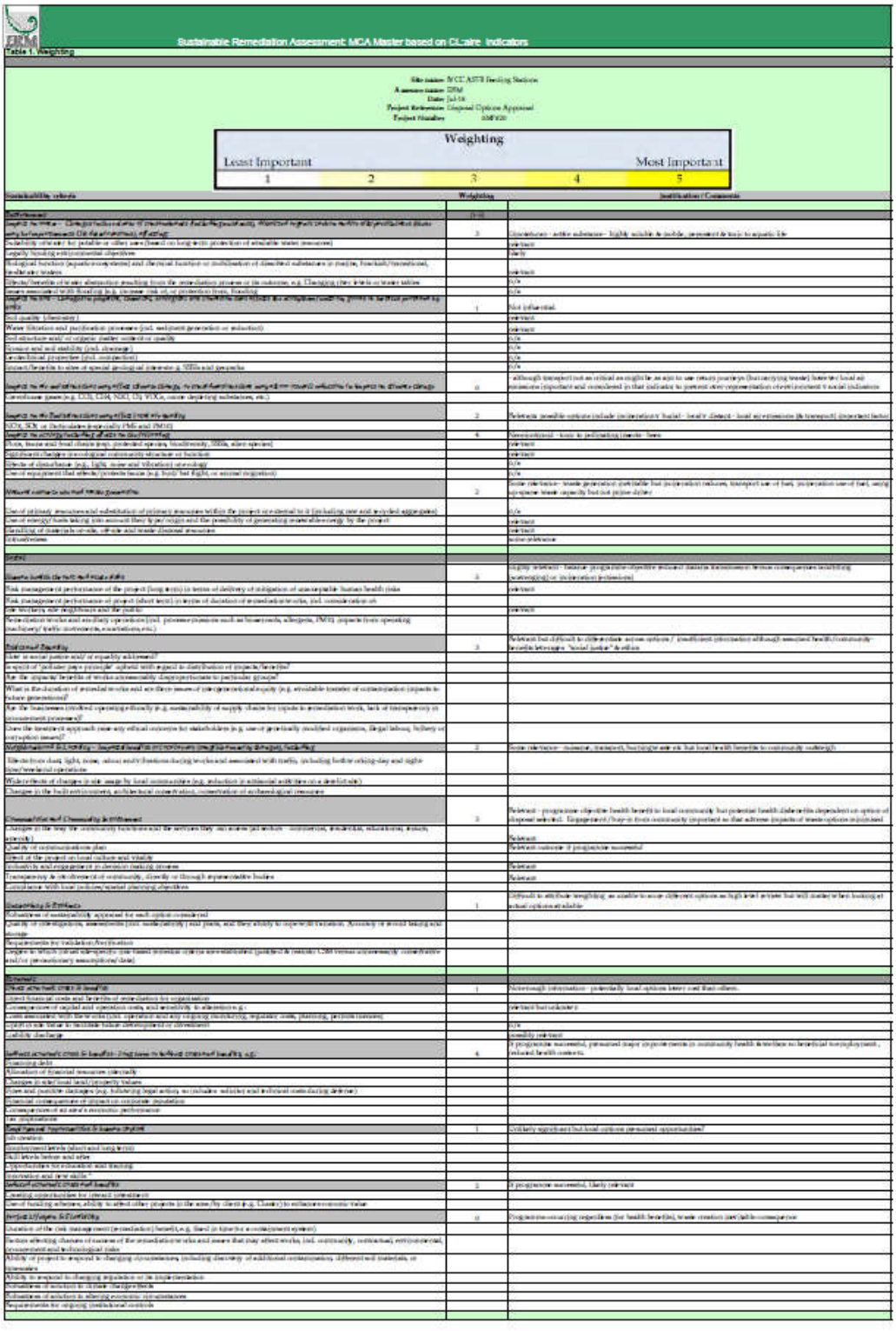
Weighting				
Least Important				Most Important
1	2	3	4	5

Next, each remedial alternative should be graded and given an overall score based upon the impact the remedial technique will have on that criterion. The following scale should be used:

Impact Severity Matrix		DURATION				
		very short	short	medium	long	permanent
MAGNITUDE	none	0	0	0	0	0
	very little effect	0	0	0	0	1
	small	0	0	1	1	2
	moderate	0	1	2	3	3
	medium	1	2	3	4	4
	large	2	3	4	5	5
	very large effect	3	4	5	5	5

The weighting and ranking exercising should be done independently of each other, that is why they are on different worksheets!

The results of the assessment will be shown in the Summary and Results worksheet. Each remedial alternative is ranked based upon the overall net sustainability benefit.



Sustainable Remediation Assessment: MCA Master based on DLaire Indicators

Table 1. Weighting

Site name: NCC ATSB Feeding Stations
Assessor name: DNM
Date: Jul-16
Project Reference: Original Options Appraisal
Project Number: 60499120

Weighting				
Least Important				Most Important
1	2	3	4	5

Sustainability criteria	Weighting	Justification / Comments
Environment	0-10	
[weight to be 0=Not relevant - 10=highest relevance of the environment] Soil quality (soil acidity, structure, organic matter, contamination) [weight to be 0=Not relevant - 10=highest relevance of the environment] Air quality	3	Groundwater - active substance - highly soluble & mobile, persistent & toxic to aquatic life
Suitability (relevance) for potable or other uses (based on long-term protection of valuable water resources)		relevant
Legally binding environmental objectives		likely
Ecological function (aquatic ecosystems) and chemical function or distribution of dissolved substances or matter, from built/transitional, ecological receptors		relevant
Effects/benefits of water abstraction resulting from the remediation process or its outcome, e.g. Changing (lowering or raising) water tables		n/a
Issues associated with flooding (e.g. increase risk of, or protection from, flooding)		n/a
[weight to be 0=Not relevant - 10=highest relevance of the environment] Air quality (dust, odour, vapour, fumes, smoke, mist)	1	Not influential.
Soil quality (chemistry)		relevant
Water filtration and purification processes (soil, sediment generation or reduction)		relevant
Soil structure and / or organic matter content quality		n/a
Erosion and soil stability (soil, drainage)		n/a
Aesthetical properties (soil, soil section)		n/a
Ground Characteristics (sites of special geological interest e.g. SSSIs and geoparks		n/a
[weight to be 0=Not relevant - 10=highest relevance of the environment] Climate change (e.g. CO2, CH4, N2O, CFCs, VOCs, ozone depleting substances, etc.)	0	Although transport not an critical an insight for an exit to see (return journeys (but carrying waste) from the local an emissions (important and considered in that indicator to prevent over representation of environment / social indicators
[weight to be 0=Not relevant - 10=highest relevance of the environment] Air quality (dust, odour, vapour, fumes, smoke, mist)	2	Relevant, possible outputs include (re-)emissions / build - local / distant - local re-emissions (ie transport) (important factor)
NOx, SOx, or Particulates (especially PM5 and PM10)		
[weight to be 0=Not relevant - 10=highest relevance of the environment] Water quality (surface, groundwater)	4	Groundwater - toxic to pollinating insects - bees
Flora, fauna and food chains (esp. protected species, biodiversity, SSSIs, alien species)		relevant
Disturbance (habitat or ecological community structure or function)		relevant
Effects of disturbance (e.g., light, noise and vibration) assessment		n/a
Use of equipment that affects (protects) fauna (e.g. bird/bat flight, or animal migration)		n/a
[weight to be 0=Not relevant - 10=highest relevance of the environment] Natural resource use (incl. land, water, materials & energy)	3	Some reduction - waste generation (verifiable but proportion reduces, transport use of fuel, proportion use of fuel, using up-to-date waste capacity but not prime driver)
Use of primary resources and substitution of primary resources within the project or external to it (including new and recycled aggregates)		n/a
Use of energy from taking into account their type and the possibility of generating more efficiently by the project		relevant
Handling of materials on-site, off-site and waste disposal resources		relevant
Groundwater		some relevance
Social		
[weight to be 0=Not relevant - 10=highest relevance of the project] Human health (short and long term)	8	Highly relevant - however, proportion of positive outputs (waste to environment versus consequences (modelling, monitoring) or intervention (emissions)
Risk management of performance of the project (long term) in terms of delivery of mitigation of unacceptable human health risks		relevant
Risk management of performance of project (short term) in terms of duration of remediation works, incl. vehicular use on site vicinity, site neighbours and the public		relevant
Remediation works and ancillary operations (incl. nuisance issues such as hours/week, allergens, PM10, impacts from operating machinery/ traffic movements, exacerbations etc.)		
[weight to be 0=Not relevant - 10=highest relevance of the project] Social equity	3	Relevant but difficult to differentiate across options / possibly not consistent although assumed health (community benefits) leverages "social justice" definition
Does it assist justice and/or equality achievement?		
In spirit of "polluter pays principle" aligned with regard to distribution of impacts/benefits?		
Are the (capacity) benefits of works unreasonably disproportionate to particular groups?		
What is the duration of extended works and are there issues of intergenerational equity (e.g. inviolable transfer of contamination impacts to future generations)?		
Are the businesses involved operating ethically (e.g. sustainability of supply chains for inputs to remediation work, lack of transparency in procurement processes)?		
Does the investment approach pose any ethical concerns for stakeholders (e.g. use of previously involved organisations, illegal labour, bribery or corruption issues)?		
[weight to be 0=Not relevant - 10=highest relevance of the project] Public health	2	Some relevance - however, transport, but might not sit, but local health benefits to continually walking/
Disturbance from dust, light, noise, odour and/or fumes including traffic and associated with traffic, including both the working day and night time/ weekend operations		
Wider effects of changes in site usage by local communities (e.g. reduction in recreational activities on a derelict site)		
Changes in the built environment, architectural conservation, conservation of archaeological resources		
[weight to be 0=Not relevant - 10=highest relevance of the project] Community/Economic Effects	3	Relevant - progressive objective (health benefit to local community) but potential health disbenefits dependent on option of disposal selected. Engagement/buy-in from community important so that adverse impacts of waste options minimised.
Changes in the way the community functions and the services they can access (eg schools - construction, evacuation, educational impact, crowds)		Relevant
Quality of communications plan		Relevant outcome if programme successful
Effect of the project on local culture and vitality		
Community and engagement in decision making process		Relevant
Transparency & involvement of community, directly or through representative bodies		Relevant
Compliance with local policies/spatial planning objectives		
[weight to be 0=Not relevant - 10=highest relevance of the project] Sustainability & Efficacy	1	Difficult to attribute weighting as unable to assign different options as high level review but will consider in fact looking at actual options available
Robustness of sustainability appraisal for each option considered		
Quality of investigations, assessments (incl. modelling) and plans, and likely ability to cope with variation. Accuracy of waste tracking and storage		
Requirements for Validation/Verification		
Degree to which private sector and/or cost based economic criteria are established (preferred) (consider LCA versus environmentally conservative and/or precautionary assumptions/data)		
Economic		
[weight to be 0=Not relevant - 10=highest relevance of the project] Direct financial costs	1	Not enough information - potentially local options lower cost than others.
Direct financial costs and benefits of undertaking for organisation		
Consequences of capital and operation costs, and sensitivity to alternatives e.g.:		Unlikely but unknown
Costs associated with the works (incl. operation and any ongoing monitoring, regulator costs, licensing, pension liabilities)		
Capital or site value to be realised (value enhancement or conversion)		n/a
Liability discharge		possibly relevant
[weight to be 0=Not relevant - 10=highest relevance of the project] Indirect economic costs & benefits - [may have to be/should consider/could be] (e.g.):	4	If programme successful, presumed major corporate events in community (health & wellbeing, beneficial employment, reduced health concerns).
Employment		
Mobilisation of financial resources internally		
Changes in wider local land / property values		
Fines and punitive damages (e.g. following legal action), as (including solicitor) and technical contributing defendant)		
Financial consequence of impact on corporate reputation		
Consequences of site and it's economic performance		
Tax implications		
[weight to be 0=Not relevant - 10=highest relevance of the project] Social Benefits & Opportunities	1	Unlikely significant but local options presumed opportunities?
Job creation		
Skills (improved levels (short and long term))		
Skill levels before and after		
Opportunities for education and training		
Incentives and new skills?		
[weight to be 0=Not relevant - 10=highest relevance of the project] Indirect economic benefits (e.g.):	3	If programme successful, likely relevant
Creating opportunities for shared amenities		
Ease of locating activities, ability to attract other projects to the area (by client e.g. Clients) to enhance economic value		
[weight to be 0=Not relevant - 10=highest relevance of the project] Project Lifespan & Flexibility	0	Programme ensuring regardless (for health benefits), waste creation inevitable consequence
Duration of the risk management (remediation / benefit) e.g. fixed or future (re-evaluation of system)		
Factors affecting chances of success of the remediation or risks and issues that may affect works, incl. commercial, environmental and technological risks		
Ability of project to respond to changing circumstances, including discovery of additional contamination, different soil materials, or timescales		
Ability to respond to changing regulations or its interpretation		
Robustness of solution to climate change trends		
Robustness of solution to altering economic circumstances		
Requirements for ongoing (institutional) controls		

Sustainable Remediation Assessment: MCA Master based on CLaire indicators

Table 2. Alternative 1

Site name: IVCC ASTB Jurding Stations
Assessor name: ERM
Date: Jul-16
Project Reference: Disposal Options Appraisal
Project Number: 0367820
Alternative 1: Option 1

Distant municipal landfill / dump site - assumed negligible engineering & people living and working on site 'scavenging' i.e. access by children, potential for indirect pollution of *sw / gw* - although spent bait station waste possible minor proportion of other wastes, potential access by pollinating insects but not high?

For each criterion give an overall score that is either positive (+) or negative (-) based upon this scale

Impact Severity Matrix		DURATION				
		very short	short	medium	long	permanent
MAGNITUDE	none	0	0	0	0	0
	very little effect	0	0	0	0	1
	small	0	0	1	1	2
	moderate	0	1	2	3	3
	medium	1	2	3	4	4
	large	2	3	4	5	5
	very large effect	3	4	5	5	5

Sustainability criteria	Option 1	Justification / Comments
Environment		
Impact on water - Changes in the release of contaminants (including nutrients), dissolved organic carbon and or all particulates (these may be improvements OR deteriorations)	-1	potential at L/F site - but also should place in context of much larger L/F site
Impact on soil - Changes in physical, chemical, biological soil condition that affects the ecosystem function, goods or services provided by soils	-1	potential at L/F site - but also should place in context of much larger L/F site
Impact on air emissions that may affect climate change, or considerations that may allow overall reduction in impact on climate change	0	transport (see below)
Impact on air emissions that may affect local air quality	-1	none, distant from community but some for transport to landfill (climate change)
Impact on ecology	-1	unlikely
Natural resource use and waste generation	-2	use of waste capacity and sterilisation of resource
Social		
Human health chronic and acute risks	2	scavenging at landfill effect to community benefit
Ethics and Equality	-1	relocating impacts to landfill
Neighbourhood & Locality - Impacts/benefits to local areas (tangible amenity changes)	-1	relocating impacts to landfill
Communities and Community Involvement	0	relocating to landfill
Uncertainty & Evidence	0	compliance? relocating to landfill
Economic		
Direct economic costs & benefits	-3	higher costs
Indirect economic costs & benefits - Long term or indirect costs and benefits	1	economic benefits of programme & removes impact from local community, ?compliance
Employment opportunities & human capital	0	removes job opportunity from local community, some with storage?
Induced economic costs and benefits	0	
Project Lifespan & Flexibility	0	n/a as weighting zero
Net environmental benefit	-4	
Net social benefit	1	
Net economic benefit	-2	
Overall net-benefit (sustainability)	**-5**	

ERM

Sustainable Remediation Assessment: MCA Master based on CL:aire indicators

Table 3. Alternative 2

Site Name: IVCC ASTB Jerding Stations
Assessor Name: ERM
Date: Jul-18
Project Reference: Disposal Options Appraisal
Project Number: 0387820
Alternative 2: Option 2
Local burial site - assumed little control - potential for direct and indirect pollution of water, access by children & access by pollinating insects + access by insects if vegetated after burial/ restoration

For each criterion give an overall score that is either positive (+) or negative (-) based upon this scale

Impact Severity Matrix		DURATION				
		very short	short	medium	long	permanent
MAGNITUDE	none	0	0	0	0	0
	very little effect	0	0	0	0	1
	small	0	0	1	1	2
	moderate	0	1	2	3	3
	medium	1	2	3	4	4
	large	2	3	4	5	5
	very large effect	3	4	5	5	5

Sustainability criteria	Option 2	Justification / Comments
Environment		
Impact on water - Changes in the release of contaminants (including nutrients), dissolved organic carbon and/or silt/particulates (these may be improvements OR deteriorations)	-3	potential - and in some localities highly likely
Impact on soil - Changes in physical, chemical, biological soil condition that affects the ecosystem function, goods or services provided by soils	-1	potential
Impact on air emissions that may affect climate change, or considerations that may allow overall reduction in impact on climate change	0	none
Impact on air emissions that may affect local air quality	0	none
Impact on ecology	-3	potential - particularly if shallow burial and revegetated
Natural resource use and waste generation	-2	sterilising local land for future use
Social		
Human health chronic and acute risks	2	children accessing local waste if left open offset against community benefit from programme
Ethics and Equality	1	local "ownership" of waste and it's disposal
Neighborhood & Locality - Impacts/benefits to local users (tangible amenity changes)	-2	impact of local burial
Communities and Community Involvement	1	community involvement required
Uncertainty & Evidence	-1	compliance?
Economic		
Direct economic costs & benefits	-2	some costs
Indirect economic costs & benefits - Long term or indirect costs and benefits	0	economic benefits of programme v. sterilisation land/ landfill legacy, compliance - fines?
Employment opportunities & human capital	1	employment opportunity?
Induced economic costs and benefits	-1	local landfill legacy
Project Lifespan & Flexibility	0	n/a as weighting zero
Net environmental benefit	-6	
Net social benefit	3	
Net economic benefit	-3	
Overall net-benefit (sustainability)	-6	

ERM

Sustainable Remediation Assessment: MCA Master based on CL:aire indicators

Table 4. Alternative 3

Site Name: IVCC ASTB Feeding Stations
Assessor Name: ERM
Date: Jul-18
Project Reference: Disposal Options Appraisal
Project Number: 0387820
Alternative 3: Option 3
[HCW Incinerator - assumed reasonable level of control/handling of waste, assumed reasonably local, high temperature / complete combustion, possible emissions but not significant?

For each criterion give an overall score that is either positive (+) or negative (-) based upon this scale

Impact Severity Matrix		DURATION				
		very short	short	medium	long	permanent
MAGNITUDE	none	0	0	0	0	0
	very little effect	0	0	0	0	1
	small	0	0	1	1	2
	moderate	0	1	2	3	3
	medium	1	2	3	4	4
	large	2	3	4	5	5
	very large effect	3	4	5	5	5

Sustainability criteria	Option 3	Justification / Comments
Environment		
Impact on water - Changes in the release of contaminants (including nutrients), dissolved organic carbon and/or silt/particulates (these may be improvements OR deteriorations)	0	none
Impact on soil - Changes in physical, chemical, biological soil conditions that affect the ecosystem function, goods or services provided by soils	0	none
Impact on air emissions that may affect climate change, or considerations that may allow overall reduction in impact on climate change	0	see below
Impact on air emissions that may affect local air quality	-1	potential for emissions but ?compliant and occurrence regardless
Impact on ecology	0	none
Natural resource use and waste generation	0	use of fuel for incinerator, handling waste but incinerating/handling waste anyway?
Social		
Human health chronic and acute risks	4	some offset of community benefit by emissions but minor
Ethics and Equality	0	neutral
Neighbourhood & Locality - Impacts/benefits to local users (tangible/amenity changes)	0	neutral
Communities and Community Involvement	0	not immediately local
Uncertainty & Evidence	0	presume compliant?
Economic		
Direct economic costs & benefits	0	
Indirect economic costs & benefits - Long term or indirect costs and benefits	2	economic benefits of programme, assumed compliance - no fines
Employment opportunities & human capital	0	neutral
Induced economic costs and benefits	0	neutral
Project Lifespan & Flexibility	0	n/a as weighting zero

Net environmental benefit	-1
Net social benefit	3
Net economic benefit	2
Overall net-benefit (sustainability)	10

ERM

Sustainable Remediation Assessment: MCA Master based on CLAIRE indicators

Table 6. Alternative 4

Site Name: IVCC ASTII Fuelling Stations
Assessor Name: ERM
Date: Jul-18
Project Reference: Disposal Options Appraisal
Project Number: 0387820
Alternative 4: Option 4
Local burning - not well controlled - may not be burnt immediately, may not be high temperature / complete combustion, likely emissions

For each criterion give an overall score that is either positive (+) or negative (-) based upon this scale

Impact Severity Matrix		DURATION				
		very short	short	medium	long	permanent
MAGNITUDE	none	0	0	0	0	0
	very little effect	0	0	0	0	1
	small	0	0	1	1	2
	moderate	0	1	2	3	3
	medium	1	2	3	4	4
	large	2	3	4	5	5
	very large effect	3	4	5	5	5

Sustainability criteria	Option 4	Justification / Comments
Environment		
Impact on water - Changes in the release of contaminants (including nutrients), dissolved organic carbon and/or silt/particulates (these may be improvements OR deteriorations)	-1	minor potential if not burnt immediately
Impact on soil - Changes in physical, chemical, biological soil condition that affects the ecosystem function, goods or services provided by soils	0	unlikely issue
Impact on air emissions that may affect Climate change, or considerations that may allow overall reduction in impact on climate change	0	local emissions
Impact on air emissions that may affect local air quality	-2	local emissions
Impact on ecology	-1	minor potential if not burnt immediately
Natural resource use and waste generation	-1	some use of fuel / waste handling
Social		
Human health chronic and acute risks	3	some offset of community benefit by local emissions/waste handling
Ethics and Equality	0	neutral
Neighbourhood & Locality - Impacts/benefits to local users (tangible amenity changes)	-1	smoke/ nuisance?
Communities and Community Involvement	1	local "ownership" of waste and it's disposal
Uncertainty & Evidence	-1	compliance?
Economic		
Direct economic costs & benefits	0	
Indirect economic costs & benefits - Long term or indirect costs and benefits	1	economic benefits of programme- compliance - fines?
Employment opportunities & human capital	0	neutral
Induced economic costs and benefits	-1	potential some minor negative consequences
Project Lifespan & Flexibility	0	n/a as weighting zero

Net environmental benefit	-3
Net social benefit	3
Net economic benefit	1
Overall net-benefit (sustainability)	**1**

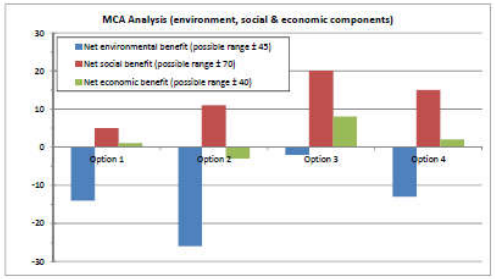
Sustainable Remediation Assessment: MCA Master based on CL:aire indicators

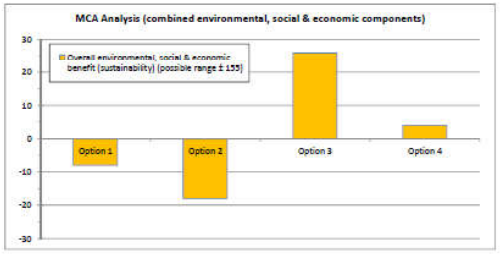
Table 10. Summary and Results

Site name: IVCC ASTB Feeding Stations
Assessor name: ERM
Date: Jul-18
Project Reference: Disposal Options Appraisal
Project Number: 387820

Sustainability criteria	Weighting	Option 1	Option 2	Option 3	Option 4
Environment					
Impact on water - Changes in the release of contaminants (including nutrients), dissolved organic carbon and/or silt/particulates (these may be improvements OR detorsorations)	3	-1	-3	0	-1
Impact on soil - Changes in physical, chemical, biological soil condition that affects the ecosystem function, goods or services provided by soils	1	-1	-1	0	0
Impact on air emissions that may affect climate change, or considerations that may allow overall reduction in impact on climate change	0	0	0	0	0
Impact on air emissions that may affect local air quality	2	-1	0	-1	-2
Impact on ecology	4	-1	-3	0	-1
Natural resource use and waste generation	2	-2	-2	0	-1
Social					
Human health chronic and acute risks	5	2	2	4	3
Ethics and Equality	3	-1	1	0	0
Neighbourhood & Locality - Impacts/benefits to local areas (tangible amenity changes)	2	-1	-2	0	-1
Communities and Community Involvement	3	0	1	0	1
Uncertainty & Evidence	1	0	-1	0	-1
Economic					
Direct economic costs & benefits	1	-3	-2	0	0
Indirect economic costs & benefits - Long term or indirect costs and benefits	4	1	0	2	1
Employment opportunities & human capital	1	0	1	0	0
Induced economic costs and benefits	2	0	-1	0	-1
Project Lifespan & Flexibility	0	0	0	0	0

	Option 1	Option 2	Option 3	Option 4
Net environmental benefit (possible range ± 45)	-14	-24	-2	-17
Net social benefit (possible range ± 70)	5	11	20	15
Net economic benefit (possible range ± 40)	1	-3	8	-2
Overall environmental, social & economic benefit (sustainability) (possible range ± 155)	-8	-16	26	-4
Rank	3	4	1	2





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16.4 ANNEX IV: ATSB HUMAN AND ENVIRONMENTAL SAFETY ASSESSMENT REPORT

Overview of human health and environmental risks of dinotefuran sugar bait feeders: Westham ATSB mosquito station

Date: 09 February 2017

Prepared for:
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Introduction

Dinotefuran is a neonicotinoid insecticide which has been identified as an effective control for mosquitos which have developed a resistance to other insecticides. The purpose of this document is to provide an initial overview of potential human health and environmental risks prior to experimental field trials.

Overview of human health risk

The use of dinotefuran in sugar feeders under normal conditions of use is not expected to present an unacceptable risk to users handling the product (placing and removing after use) or to residents living in the community.

Dinotefuran is contained between a polyester/polyethylene laminate and an impermeable film membrane. There is not expected to be any leakage of dinotefuran to the surface of the film (see overview of environmental risk below). Thus, the bait station (product) can be handled safely providing that the integrity of the product is maintained. It will be positioned out of reach of young children and therefore the risk of tampering and possible inadvertent exposure from misuse is considered to be low.

However, as a worst case assessment it is assumed that a child may get hold of one or more products and deliberately break them open to ingest the sugar bait. Each product contains 100 g of sugar/fruit juice solution and 0.1% dinotefuran (0.1 g). The following assessment calculates the maximum amount of sugary fluid that can be ingested before exceeding the acute reference dose (ARfD) or the rat LC_{50} value for dinotefuran (1.25 mg/kg bw and 2000 mg/kg bw, respectively; US EPA Fact Sheet, 2004 and Durkin, 2009[1]).

$$= \frac{\text{ARfD (mg/kg bw) x bodyweight (kg) x 100}}{\text{Concentration of a.s. in product (\%)}}$$

$$= \frac{\text{1.25 (mg/kg bw) x 10 (kg)}^2 \text{ x 100}}{\text{0.1 (\%) x 1000}}$$

= 12.5 g of sugary fluid

In this worst case scenario the ARfD would be exceeded 8-fold if the whole content of one bait station was consumed. This represents a risk of a potential adverse effect and therefore, it will be important to mitigate the risk by good product stewardship and education of the community. It is unlikely to lead to a significant poisoning incident given the margin of safety built into the ARfD. The potential for acute poisoning can be calculated by estimating the maximum amount that could be ingested at the rat LC_{50} of 2000 mg/kg bw. The ARfD is replaced by the LC_{50} in the above calculation.

$$= \frac{\text{2000 (mg/kg bw) x 10 (kg)}^1 \text{ x 100}}{\text{0.1 (\%) x 1000}}$$

= 20,000 g of sugary fluid (200 bait stations)

[1] P. R. Durkin, Dinotefuran: Human health and ecological risk assessment, Syracuse Environmental Research Associates Inc., Fayetteville, New York, USA, 2009.
http://www.fs.fed.us/foresthealth/pesticide/pdfs/0521803b_Dinotefuran.pdf

[2] Child body weight (1 to ≤3 years) from EU EFSA resident model

Ingestion of this amount would be impossible as an acute event. If it is assumed that a child maybe 10 times more sensitive than a rat then the maximum number of ingested bait stations that could lead to severe poisoning would reduce to 20. Even in this case a severe poisoning incident with a child is considered to be highly unlikely, again assuming good product stewardship practices are in place (e.g. locked storage facilities and contained disposal procedures).

Conclusion for human health

The human health risks of potential exposure to dinotefuran ASTB mosquito stations are considered to be low under normal use conditions. Adverse health incidents from possible misuse / abuse of the product are unlikely with good product stewardship.

Overview of environmental risk

As a neonicotinoid, the use of dinotefuran for the control of mosquitos raises potential concern for other non-target arthropods such as bees which are known to be sensitive to this class of insecticides.

The design of the sugar feeders in the ATSB mosquito station is intended to allow exposure to mosquitos and limit exposure to other arthropods. The film in the feeders which contains the dinotefuran is designed to allow puncture by piercing mouth parts only, such as the proboscis of the mosquito. The film rapidly re-seals once the proboscis has been removed to prevent the treated sugar fluid pooling out onto the surface of the feeder where it could be available to other arthropods, such as honey bees. The designed dark colour of the feeder is also not intended to be attractive to flower pollinating arthropods. A range of other arthropods have comparable biting mouth parts to the mosquito, such as the horse fly or sucking mouth parts such as those found on hemipteran (e.g. shield bugs) which are designed to pierce leaves to extract sap. Wasp and bees could also potentially have exposure to the sugar fluid from the feeding if any fluid did leak onto the feeder surface. To assess the potential for exposure of non-target arthropods to the fluid within the sugar feeder a sampling survey has been conducted. The study was conducted in 14 villages where the feeding stations were hung as intended for mosquito control. The feeding solution was stained with a tracer dye which could be detected in bodies of any arthropods which had been able to feed on the stained bait. Arthropod sampling traps were placed to sample the overall diversity of arthropods in the vicinity of the traps and to determine the relative proportion of individuals which could be identified to have fed on the stained bait. The results of the sampling survey are summarised in the following table.

Table 1. Summary of arthropod sampling and proportion of those arthropods identified to have fed on the feeding station

Group	Morpho-species Identified from total 14 villages	N of selected & dissected sub-samples on villages basis	% of dissected samples fed on stained bait
Hymenoptera			
Honey bees	1 species (African Honey Bee)	150 - 250	0 - 2%
Wild Bees	>65 species	300 - 500	0 - 1.0%
Wasps general	>280 species	250 - 500	0 - 1%
Social Wasps	> 74 species	(included in general wasp sample)	0 - 3%
Parasitic wasps	> 171 species	100 - 250	0 - 1.5%
Ants	> 15 species	200 - 300	0
Lepidoptera			
Rhopalocera	> 92 species	100 - 300	0 - 0.1%
Sphingidae	> 24 species	50 - 100	0 - 0.1%
"Bombyces" complex	> 187 species	100 - 400	0 - 1%
Noctuoidea	> 305 species	300 - 1000	0 - 1%
Geometroidea	> 160 species	200 - 300	0 - 1%
Pyraloidea	> 213 species	200 - 400	0 - 0.5%
Coleoptera			
Carabidae	> 350 species	100 - 400	0 - 0.5%
Tenebrionidae	> 43 species	100 - 800	0 - 0.5%
Scarabaeidae	> 150 species	100 - 200	0 - 1%
Cerambycidae	> 27 species	30 - 200	0 - 2%
Chrysomelidae	> 55 species	100 - 300	0 - 1.5%
"OTHER" beetles	> 450 species	300 - 1000	0 - 2%
Diptera			
Brachycera	>485 species	400-2000	0 – 2.5 %
Chironomidae	Approx. 10 species	200-300	0- 6%
Hemiptera			
Cicadomorpha	>124 species	50-100	0-0.3%
Heteroptera	>290 species	100-300	0-0.5%
Orthoptera			
Caelifera	>65 species	50-400	0-0.3%
Ensifera	>32 species	50-100	0-1%
Neuroptera			
Myrmeleontiformia	>35 species	20-200	0-1%

In total over 3700 species were identified in the sampling survey from 7 different orders and 27 suborders. A wide variety of arthropods with a range of feeding strategies were therefore considered to be covered. The number of selected and dissected sub-samples assessed from each of the villages ranged from 50 – 2000. The

percentage of dissected samples which were identified to have fed on the stained bait were shown to be very low and typically ranged from 0 - 2%. Marginally higher proportions of social wasps, up to 3 %, and chironimidae (non-biting midges) up to 6 % were identified to have fed on stained bait. The low exposure to the bait would not have a significant effect on the overall populations of these groups. This indicates that the ASTB feeding stations were either unattractive for feeding to these arthropod groups, or the design of the feeders significantly limited the potential for non-target arthropods to feed on the treated bait.

Conclusion for non-target arthropods

Based on the results of the broad arthropod survey which covered a wide variety of species, the relative proportions of those samples which were identified to have fed from the feeders were shown to be minimal. It can therefore be concluded that the design of the ATSB feeding stations significantly limits exposure of the treated bait to non-target arthropods. Exposure to dinotefuran from this design would therefore be limited and not expected to have a significant effect on non-target arthropod populations under normal conditions of use.

The possible environmental risks arising from misuse / abuse of the product (eg. disposal in water bodies) can be estimated if required.