Master Statistical Analysis Plan ATSB Phase III Trials

Section 1: Administrative Information

Title and trial registration

Attractive Targeted Sugar Bait (**ATSB**) Phase III Trials in Kenya, Mali, and Zambia

Trial registration numbers

Mali - ClinicalTrials.gov Identifier: NCT04149119

Zambia -

Kenya -

Statistical Analysis Plan version

SAP version number 4.0 March 8 2021

Protocol version

Relates to Protocol version March 8 2021 - Attractive Targeted Sugar Bait Phase III Trials in Kenya, Mali, and Zambia - Master Protocol

SAP revisions

Version Number	**Revisions on Previous**	**Date of revision**	**Timing of Revision in relation to study**	**Rationale**
Version 1.0	NA	September 26th 2020	Pre study initiation	First Version
Version 2.0	Response to VCAG review	January 21st, 2021	Pre-study initiation	Address VCAG review
Version 3.0	Incorporation of team review prior to VCAG resubmission and DAC review	February 5th, 2021	Pre-study initiation	Preparation for VCAG resubmission and DAC review
Version 4.0	Incorporation of team review and DAC comments	March 8th, 2021	Pre-study initiation	Final draft for VCAG review and endorsement

VCAG: World Health Organization Vector Control Advisory Group

DAC: Design, Analyze, and Communicate Team commissioned by the Bill and Melinda Gates Foundation to review the study protocol.

Roles and responsibility

Name	Affiliation	Role in SAP
Joshua Yukich	Associate Professor, Tulane University School of Public Health and Tropical Medicine	Lead SAP author
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Signatures:

Person writing the SAP

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Senior statistician responsible

TBD

Chief investigator/clinical lead

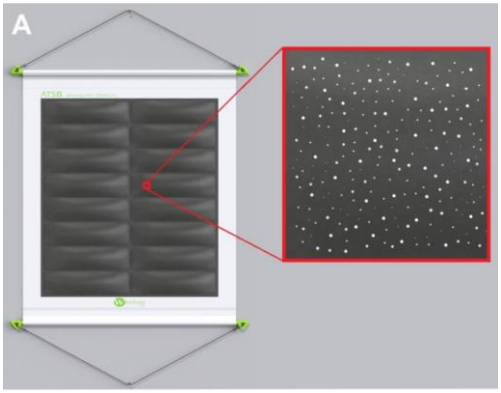
Section 2: Introduction

Background and rationale

Highly effective interventions against malaria vectors that preferentially feed on humans late at night and rest inside houses have been developed and implemented at scale. Their effectiveness is a function of the fact that they specifically target indoor-biting and indoor-resting mosquitoes, which are often the same mosquito species comprising the bulk of the vectorial system.

However, several mosquito species have evolved high levels of resistance to the insecticides used in LLINs and IRS as result of prolonged exposure through the scale up of these interventions. There is increasing concern that this insecticide resistance is undermining the effectiveness of these interventions. Furthermore, malaria vectors exhibit different behavioral characteristics that mitigate the effectiveness of vector control strategies and these too may respond dynamically to interventions targeting indoor behaviors.

In addition to the biological need for female *Anopheles* species to take a blood meal to obtain protein necessary for egg production, all *Anopheles* must feed regularly and frequently on liquid and carbohydrates (sugars) to survive. Mosquitoes are guided to sugar sources by chemical attractants. The ATSB (Attractive Targeted Sugar Bait) is designed specifically to attract the mosquito with a source of liquid and sugar and include an ingestion toxicant to then kill the mosquito. Using sugar sources to attract mosquitoes to an ingestion toxicant is a relatively simple and inexpensive strategy that has been shown to be highly efficacious for mosquito control in a limited number of trials.



Westham Co. developed a bait station that contains a plant-based mosquito attractant, sugar as a feeding stimulant, and an active ingredient (the neonicotinoid, dinotefuran) to kill the foraging vectors. The bait additionally 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 station has a protective membrane that covers and protects the bait from rain and dust, but that allows mosquitoes to feed through it (See Figure A). Durability studies conducted in Mali, Kenya, and Zambia in 2019 showed that the Westham ATSB can remain effective in the field for at least six months. The protective membrane allows mosquitoes to feed, but it serves as a barrier to pollinators. Field studies to-date have also shown that the ATSB has a minimal impact on non-target organisms. This includes evidence specifically for the toxicant that will be used, dinotefuran. An initial environmental assessment and subsequent field trials in Mali have demonstrated that when deployed within the ATSB, the toxicant does not pose safety risks to non-target organisms, including pollinators and humans (unpublished data, personal communication with GC Muller).

The Westham ATSB was selected based on results from early testing of bait stations in Israel and Mali. In these studies, bait stations with a food dye marker (without toxin) established that large proportions of the mosquito population were marked daily by the food dye. Proof of concept studies for impact on mosquito vectors in Mali began in 2015 with a collaborative team

from Hebrew University, University of Bamako, University of Miami, Tel Aviv University, and University of Haifa. Results thus far demonstrate that the ATSB has the desired impact on mosquito vector populations. Research beginning in early 2017 incorporated the toxicant dinotefuran into the bait stations. Early entomological results indicate that outdoor use of ATSBs reduces vector abundance and skews the adult age distribution towards younger mosquitoes. Recent field studies in Mali concluded in early 2018 examined the impact of the ATSB on entomological measures and established an optimal deployment pattern for the local setting. This deployment protocol of two ATSBs installed on opposite exterior walls of sleeping structures at a height of 1.8 meters was associated with a target mosquito feeding rate of at least 30%. The drastic reduction in mosquito density, number of older females, and number of sporozoite infected females, and entomological inoculation rate suggest that the ATSB can significantly reduce malaria parasite transmission (Traore *et al* 2020).

Modelling of ATSB study data suggest that ATSBs could markedly reduce mosquito populations across a range of different transmission intensities and should have great potential when used in combination with other indoor vector control tools.

The World Health Organization Vector Control Advisory Group (VCAG) reviewed these data and recommended the evaluation of the potential of the Westham ATSB to reduce clinical malaria incidence in different transmission settings in sub-Saharan Africa. This SAP is intended to serve as a master SAP for each of three trial sites in Kenya, Mali, and Zambia. Three harmonized clinical trials will use this master plan as the basis of a site specific SAP which may contain minor modifications to adhere to site specific nuances, including but not limited to, changes in covariables included in analysis or definitions and cutoffs of said variables and summary measures. While the intent of the harmonization is to largely ensure that the trial analysis is conducted comparably and identically the site-specific SAPs will require minor modifications.

Description of research objectives

Primary Objective:

(1) To evaluate the efficacy of ATSB deployment plus universal vector control coverage (IRS or LLIN) coverage after two transmission seasons on a minimum 30% reduction in population-based cohort clinical malaria incidence as compared with universal vector control coverage alone.

Secondary Objectives:

(2) To evaluate the efficacy of ATSB deployment plus universal vector control coverage (IRS or LLIN) coverage on a minimum 30% reduction in community parasite prevalence as compared with universal vector control coverage alone.
(3) To evaluate the efficacy of ATSB deployment plus universal vector control coverage (IRS or LLIN) coverage on passively-detected confirmed malaria case incidence as compared with universal vector control coverage alone.
(4) To evaluate the efficacy of ATSB deployment plus universal vector control coverage (IRS or LLIN) coverage on time to first infection as compared with universal vector control coverage alone.
(5) To assess a minimum set of entomological outcomes that measure ATSB efficacy in reducing the target vector population.
(6) To assess the acceptability of ATSBs by communities and other stakeholders. This includes identification of potential barriers to uptake and consistent ATSB coverage, together with assessment of ATSB impact on coverage and use of existing malaria control interventions (e.g. LLIN use, treatment-seeking behavior).

(7) To estimate the cost and cost-effectiveness of deploying ATSBs for malaria control.
(8) To assess the safety of ATSBs on humans by monitoring adverse effects in communities where ATSBs are deployed compared to the control.

Research questions and hypotheses

Primary research question:

(1) Is outdoor deployment of ATSBs plus universal vector control coverage (LLIN or IRS) more effective than universal vector control coverage alone at reducing cohort-based clinical malaria incidence over a two-year period?

Secondary research questions:

(2) Is deployment of ATSBs associated with a reduction in community parasite prevalence?
(3) Is deployment of ATSBs associated with a reduction in passively-detected confirmed malaria case incidence?
(4) Is deployment of ATSBs associated with a reduction in time to first infection?
(5) Is deployment of ATSBs associated with a decline in malaria vector densities (particularly among older females), longevity (parity status or proportion of females with three or more gonotrophic cycles), sporozoite rates, and EIR?
(6) What are the barriers to high ATSB coverage?
(7) Does ATSB deployment affect LLIN use?
(8) What is the cost and cost-effectiveness of outdoor ATSB deployment as a vector control intervention?

Section 3: Study Methods

Trial design

An open-label two-arm cluster randomized controlled trial (CRCT) design will be used comparing ATSB + universal coverage with a WHO core VC intervention vs universal coverage with VC alone (standard of care). The trial will follow a group-sequential design (Pocock 1977) with one (two in Kenya) potential interim analysis. Three stand-alone superiority CRCTs will be conducted, one in each of Kenya, Mali and Zambia with design and methods standardized across sites. Each trial will be have sufficient power to answer the question for that setting. Universal VC (mainly LLIN) will be ensured in both arms prior to start of the study and will serve as the standard of care. Arm 1 will receive ATSBs for up to two years. Arm 2 will receive the standard of care of universal vector control coverage.

Randomization

Restricted randomization will be used to randomize study clusters to intervention and control arms with balance between study arms on key baseline characteristics, including the primary outcome. The steps one through five below to achieve restricted randomization will be carried out by a member of the study team that is not responsible for trial implementation. Steps six and seven below (random selection of a specific allocation sequence (randomization) and assignment of arms to intervention or control) will be conducted by an independent community member or statistician not associated with the trial. Steps one to six of the randomization will be conducted independently for each study site by the designated lead trial statistician for each of the trials after the central development of a randomization program that is vetted by a designated statistician for each study site. The steps for randomization are as follows:

1. Establish balance criteria. The factors described in Table 1 below may be considered for suitability as restriction criteria. This list is suggestive rather than prescriptive and specific criteria and restriction limits will vary by study site. Criteria for determining balance will be varied during the restricted randomization process to both ensure balance and the validity and lack of bias in study design.

Table 1. Covariates to be considered for restricted randomization

Covariate/ endpoint	**Restriction criteria**	**Data source**	**Analytic method**
Malaria disease incidence	Difference in mean clinical case incidence between trial arms (size of difference to be assessed when data are available)	Baseline cohort	Difference in disease incidence of cluster summaries between study arms
Bednet use	Difference in mean proportion of persons slept under any net night before survey between trial arms ≤5 percentage points	Baseline survey	Difference in means of cluster summaries of proportion of persons of all ages slept under any net night before survey between arms
Population	Total population size of larger trial arm no more than 10% larger than smaller arm	Enumeration datasets	Sum(pop size of clusters Arm large)/Sum(Pop size of clusters arm Small) less than 1.10
Urbanization*	Number of urban clusters in each arm nearly balance	Census data using national classification (alternatively remote sensed classification could be used (GRUMP/WorldPop)	N in arm A ± 1 of N in Arm B
Housing density*	Difference in mean housing density between trial arms ≤ 0.3 SD of overall cluster level housing density	Enumeration + cluster boundaries GIS files Or Remote 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 nearly balanced across arms	Study team documentation	N in arm A ± 1 of N in 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) shape files for cluster boundaries.	SD(cluster estimates of altitude)*0.3 ≥ |mean(cluster estimates of altitude Arm a) – mean(Cluster estimates of altitude Arm b)|

Covariate/ endpoint	Restriction criteria	Data source	Analytic method
Entomological data collection	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.

2. Generate a list of at least 100,000 randomizations (Allocation sequences)
3. Check randomizations (allocation sequences) against balance criteria and drop those that do not fit
4. Assess the number of randomizations (allocation sequences) remaining. If fewer than 10,000 acceptable randomizations (sequences) remain stop and relax restriction criteria. If a high proportion of allocation sequences remain (*e.g.* >90%) consider tightening balance criteria.
5. Test remaining set of potential randomizations (allocation sequences) for validity, specifically that all clusters are being independently assigned to study arms (*i.e.* check that no two clusters are always jointly assigned to the same or always to opposite arms, more stringent criteria such as clusters occurring jointly in too small a proportion (*e.g.* 1/10,000) allocation sequences can also be applied).
6. Randomly choose a randomization (allocation sequence).
7. Flip a coin to determine if arm A or arm B is ATSB or control.
   Note: Step 6 and 7 to be done in public with community participation.

After allocation, the intervention will be implemented in the entire ATSB arm according to assignment. Allocation of study arms will not be blinded to the participants, the deliverers of the intervention, or to the main investigators (but will be to lab workers carrying out tests on blood samples and mosquitos). Sham bait stations will not be used in control areas.

Sample size

Full details of the sample size calculations are contained in the trial master protocol and study site specific protocols.

Case incidence cohort

The sample size calculations for the case incidence cohort were calculated using the formula for cluster randomized trial event rates with a person-time denominator (Hayes and Moulton 2017). Assumptions utilized in the calculations are summarized below. These assumptions are based on data from similar studies conducted in comparable settings for each study site. In each case, the calculation was completed for person-time required to demonstrate superiority with a 30% reduction in cumulative clinical case incidence of malaria over a two-year period. Note that cohort follow-up time differs across the sites. A seasonal cohort will be implemented in Mali (8 months of follow-up) and Zambia (6 months of follow-up). In Kenya, the cohort study will run continuously for the 2-year period, however the cohort will be rotated every 6 months (*i.e.* each individual will be followed for up to 6 months).

Table 2: Sample Size for incidence

	Kenya	**Zambia**	**Mali**
Clusters per arm (overall)	40 (80)	40 (80)	38 (76)
Trial duration in calendar years (seasonality of FU) (total FU per participant time in months)	2 years (12-month seasons) (24 months FU)	2 years (6-month seasons) (12 months FU)	2 years (8-month seasons) (16 months FU)
α (Type 1 error probability for two year trial)	0.044 (O'Brien Fleming with two interim analyses at approx. 50% and 75%)	0.049 (O'Brien Fleming with one interim analysis)	0.049 (O'Brien Fleming with one interim analysis)
β (Type 2 error probability for 2 year trial)	10% (90% power)	10% (90% power)	10% (Power=90%)
baseline incidence of clinical malaria in the target age group	0.845 events per person year during a 12m malaria transmission season (12m- <15y)[1]	0.4 events per person-year (based on 0.8 incident events during a 6-month malaria season) (12m- <15y)	0.4 events per person year (based on 0.6 incident events during an 8-month malaria season) (5y-<15y)
reduction in baseline incidence	30% (i.e. incidence rate ratio = 0.70)		
coefficient of variation	0.40	0.40	0.40
Assumed loss of person time, including true LTFU plus loss due to exclusion of 2w person time following each treatment with AL	20%	20%	20%
Total person years per cluster per year before adjustment for loss-to-follow-up	15 obtained by recruiting 30 individuals for 6 months each	29, obtained by recruiting 58 individuals for 6 months each	25.3, obtained by recruiting 38 individuals for 8 months each
Total person-years per clusters over 2 years before adjustment for loss-to-follow-up	30 (30x[6/12]x2)	58 (58X[6/12]x2)	50.67 (38x[8/12]x2)

	Kenya	Zambia	Mali
Total person-years over 2 years before adjustment for loss-to-follow-up	2,400 (80x30x[6/12]x2)	4,640 (80x58x[6/12]x2)	3,850 (76x38x[8/12]x2)
Total person-years per cluster available for analysis	24 (0.8x30x[6/12]x2)	46.4 (0.8x58X[6/12]x2)	40.5 (0.8x38x[8/12]x2
Total person-years available for analyses	1,920 (0.8x80x30x[6/12]x2)	3,712 (0.8x80x58x[6/12]x2)	3,080 (0.8x76x38x[8/12]x2)

1 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 to account for an anticipated 25% reduction in clinical malaria in children 1-<5 years of age (28.6% of the sample study cohort) due to the implementation of the RTS,S/AS01$_E$ vaccine in two-third of the study area (resulting in an estimated 7.4% reduction in event rates in children 1-<15 years), 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.

Cross-sectional household survey

The sample size calculations for the parasite prevalence surveys were calculated using the formula for cluster randomized trial proportions (Hayes and Moulton 2017). Sample size calculations for each site were completed using PASS 15 Sample Size Software (©NCSS, Kaysville, Utah) for Kenya and Zambia, and R (© The R Foundation) for Mali all calculations follow formula from (Hayes and Moulton 2017).

Table 3: Sample Size for prevalence outcomes:

	Kenya	Zambia	Mali
Cluster per arm	40	40	38
α	0.049 (two-tailed)		
β	0.20 (90% power to detect a significant difference)		
baseline parasite prevalence measured by RDT among people age 6 months and older	29.0%[1]	42.8%	50%
reduction in baseline prevalence	30%		
ICC = intracluster correlation coefficient (coefficient of variation)	0.07	0.12	0.16 (cv = 0.4)
Non-response	20%	10%	20%
individuals sampled	48 per cluster per year Total of 3,840per year	59 per cluster per survey Total of 4,720 per round	32 per cluster per survey Total of 2,432 per round

1 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, its 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%).

Passive case detection

Data from all health facilities regarding people of all ages will be used to calculate confirmed malaria case incidence in the intervention and control clusters. In seasonal sites (Mali, Zambia) incidence data collection will coincide with prespecified seasons where ATSB deployment is assumed to occur prior to the start of the season. In Kenya specific dates for data collection will be specified in study site specific ATSB in terms of timing of data collection/analysis start after ATSB deployment (*i.e.* a wash-in period of ~ 2 weeks after ATSB deployment may be included and should be precisely pre-specified in Kenya site specific SAP).

Framework

The trials are planned under a superiority framework. The comparisons will consist of two-sided tests of the null hypothesis that the outcomes in the ATSB (intervention) arm are statistically indistinguishable from the outcomes in the control arm. All primary comparisons will consist of comparisons of the outcome in the intervention arm vs. the outcome in the control arm.

Statistical interim analyses and guidance

One possible interim analysis is planned in Mali and Zambia. In Kenya, an additional (second) interim analysis is planned because this trial lasts six months longer than the other two trials because transmission occurs throughout the year in Kenya. In Kenya, the interim analyses will be event, rather than time, driven. In Mali and Zambia, the interim analysis will be conducted at the end of the first transmission season in the first year.

In Kenya, 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=415) and 75% (n=622) of the total number of expected primary outcome events over two years in the control arm (n=829) have occurred (whichever comes first). The number of events will be tracked by an independent statistician not involved in the trial. In Zambia and Mali an interim analysis will be conducted after the first transmission season regardless of the total number of events.

The interim analysis will consider a stringent rule in each site based on the Lan-DeMets spending function with O'Brien-Fleming type boundaries to preserve the overall two-sided type I error rate for efficacy at the α=0.05 level at the final analysis. Should the results of the interim analysis result in a decision to continue the trial, the final null-hypothesis significance testing will be conducted with alpha levels of 0.049 (a total of two looks) instead of 0.05 in Mali and Zambia, and 0.044 in Kenya (total of three looks) in order to control the overall type-I error potential in the trial.

Each study site DSMB will be responsible for determining when an interim analysis is required per trial rules. If an interim analysis is indicated, the DSMB will conduct formal tests of the study data against the following rules:

Firstly, the trial statistician will develop the analysis programs for 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 prior to the scheduled DSMB meeting. The DSMB statistician receives copy of the random treatment assignment code directly either 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.

Overwhelming benefit rule:

The DSMB may consider recommending an early submission of the ATSB dossier for overwhelming benefit if a test of the null hypothesis that the cumulative clinical incidence of malaria in the intervention arm in the intention to treat analysis population is significantly lower than the cumulative clinical incidence in the intention to treat analysis population of the control arm at a significance level < 0.003 after the first or only interim analysis, and 0.0183 after the second interim analysis (Kenya only). This test will be conducted using a variance components regression model with a Poisson likelihood and a log link function which includes random cluster level intercepts. The regression will include a fixed effect for study arm, and the hypothesis will be tested by testing that the incidence rate ratio associated with this covariate is not significantly different than 1 with a *p*-value < 0.003 (for the first interim look) and <0.0183 (for the 2nd interim look), respectively.

The DSMB recommendation will not be based solely on the results of this statistical test. The DSMB can advise continuing the trial even if statistically the boundary is crossed, *e.g.,* in order to continue collecting more epidemiological, entomological, or safety information or data for further sub-group analyses. It is the intent of the investigators to continue the trial in the case of early efficacy demonstration.

Stopping for harm:

The trials do not include formal stopping rules based on harm, because the intervention is not targeted to humans and the expected risk to trial participants is expected to be minimal; thus formal harm-based stopping rules are not needed. However, this does not preclude the DSMB stopping the trial for harm should unforeseen consequences of the ATSB or trial procedures lead to harms. For example, deliberate abuse or misuse of the ATSB products, unforeseen non-target insect impacts, could lead to harms which cause trial stoppage.

Timing of final analysis

Should no early stopping rule be invoked and the trial continue after each interim analysis, then the final analysis per trial (country) will be conducted collectively at the end of two seasons/years. This analysis will occur at the site level. A final pooled individual participant data (IPD) analysis and meta-analysis of trial outcomes will be conducted collectively after the termination of the trial in all study sites.

Timing of outcome assessments

Primary and secondary efficacy outcomes

Primary outcome

The primary outcome measure is the incidence rate of clinical malaria defined as history of fever or a measured temperature ≥37.5C and a positive malaria rapid diagnostic test (RDT) (The definition is specified in full in a later section). This will be assessed among people aged 12 months to less than 15 years (≥5y to 15y in Mali). These outcomes will be ascertained from monthly follow-up visits to cohort study households. Visits will be conducted within ±5 days for true monthly intervals and specific follow up time between visits will be computed to the nearest one day.

Secondary outcomes

1. Time to first infection assessed among the cohort by PCR. This will be assessed monthly as per the primary outcome.

2. Prevalence of malaria infection among participants aged six months and older, detected by RDT. This outcome will be assessed annually cross-sectionally (or through a rolling prevalence survey in Kenya). For the s cross-sectional analyses (Zambia, Mali), measurement will occur in each member of the study sample within an approximate one-month (30-day) window.

3. Incidence rate of passively reported clinical malaria among participants of all ages, defined as the number of malaria confirmed cases (by RDT or microscopy), linked to study clusters by place of residence, per 1,000 population per year, using routine data from health facilities serving the study population (*e.g.* by name of village of residence) and cluster population sizes for the denominator. This outcome is assessed daily at routine health facilities and dispensaries, but analysis will occur as part of the collective analysis at trial end.

Section 4: Statistical Principles

Confidence intervals and *p*-values

The trial is generally intended to control type-I error to less than 5%. As such, given the planned interim analyses at each trial site, type-I error will be controlled using an O'Brien-Fleming type error spending function as discussed above. The main trial results (treatment efficacy estimates) will be presented with 95% confidence intervals and *p*-values.

Adherence and protocol deviations

Since the intervention is deployed on a group basis rather than individually, adherence definitions will take account of this. Standard adherence will be defined as intention to treat a cluster of residence with ATSBs. Individual adherence will be defined based on ATSBs present at individuals' households. 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.

Standard adherence will be defined as intention to treat a cluster of residence with ATSB. The per-protocol analysis populations will be defined as those living in intervention clusters where ATSB was deployed and replaced according to planned schedule. Clusters where more than

one-month delay in ATSB deployment occurred or where substantial deployment of ATSB into control areas occurs (*e.g*. deployment consistent with distribution of ATSB to control areas) will be removed from the per-protocol analysis population.

Standard protocol deviations will be considered reportable/summarizable when clusters refuse placement of ATSB despite having been assigned to intervention arm and providing initial study consent. Additionally, protocol deviations will be considered to have occurred if ATSB replacement visits by the study team are delayed by more than three weeks from the expected timeline according to study planning. 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 result in a delay of primary outcome assessment of greater than two weeks.

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

Analysis populations

There are two analysis populations for the primary outcome assessment: These are the intention to treat population and the per-protocol analysis population. The intention to treat population consists of all eligible individuals recruited and consented to participate in the study. The primary analysis will be conducted on the intention to treat population. Per-protocol analysis populations will be those eligible, recruited and consented individuals whose adherence cluster level meets the adherence standard. Entomology results collected during the trial may also be used to inform further definition of the per-protocol population prior to data lock. The DSMB will also be requested to provide advice on formal per-protocol population definitions following baseline analysis.

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.

Section 5: Trial Population

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 population to be sampled for outcome assessment considers several additional inclusion and exclusion criteria for inclusion in the cohort studies as outlined below.

Screening data

Since the trial is conducted as a cluster randomized study no individual screening is conducted. Trial areas will be enumerated prior to cohort enrollment and the enumeration will identify households with residents that meet eligibility criteria for cohort participation and for eligibility for inclusion in cross-sectional household samples (e.g. eligible aged children for outcome assessment). Cluster level screening is anticipated to be conducted during a baseline period in each study site. A larger number of clusters than planned for the final study power will be included in each site (~10% extra clusters). These clusters will be included in baseline data collection but excess clusters will be excluded prior to randomization. Exclusion will consider the following criteria: malaria prevalence and incidence defined as per primary and secondary trial

outcomes (with a specific aim to exclude any clusters found to have zero or near zero malaria incidence or prevalence in the baseline period or those with dramatically higher incidence/prevalence as compared to other study clusters). Additionally, logistic feasibility of implementation will also be considered with clusters in which implementation of intervention or data collection is determined to be impracticable, to be considered for exclusion.

Eligibility

Eligibility for participation is described in detail in the protocol but in short, in the cohort monitoring requires that the individual resides in the study areas within the core sampling areas and additionally is a:

- Household resident
- At least 12 months of age and less than 15 years of age at the time of enrollment (≥5 to 15 in Mali).

And is not a:

- Resident whose home is located within a buffer zone
- Pregnant at the time of cohort enrollment.
- Pregnant at any time during the cohort study.

Recruitment

Recruitment into the cohort study will be conducted by first completing an enumeration of all households and their members in the study clusters. This enumeration will be used as a sampling frame to select households with eligible individuals for the cohort study. Within each study cluster, a simple random sample of households with eligible individuals will be selected. Within clusters, sampling for the cohort study will exclude people living in households within a geographic buffer zone around the perimeter of the cluster. Further details of recruitment are contained in the master trial protocol.

The CONSORT diagram will include at minimum the following elements.

Table 4: CONSORT diagram contents

Cohort Study (For each cohort)	**Cross sectional study (each round)**
Number of study clusters (by arm)	Number of Study clusters (by arm)
Number of sampled houses (by arm)	Number of Sampled houses (by arm)
Number of consented participants (HHs with participants) (by arm)	Number of consenting houses (by arm)
Number of participants (HHs) randomized to each study arm	Number of completed interviews (by arm)
Number of monthly follow up visits conducted (by arm)	Number of tested individuals (by arm)
Number of missing HH monthly visits (by arm)	Number of Incomplete HH surveys (by arm)
Number of participants (HH) lost completely to follow up (by arm)	Number of identified eligible participants not tested (by arm)
Number of participants (HH) completing (by arm)	

Withdrawal/follow-up

It is anticipated that there will be approximately 20% LTFU withdrawal from each cohort. This is accounted for in sample size calculations. Level of non-participation in the household surveys is expected to be 10-20%. LTFU will be summarized by arm and by cluster.

Baseline patient characteristics

The study anticipates summarizing a number of baseline participant characteristics at the individual, household and cluster level. The following table lists these minimum baseline participant characteristics and the expected summary measures which will be summarized in the cohort and cross-sectional surveys.

Table 5: Baseline patient characteristics (Table one contents)

Characteristic	**Cohort summary measure**	**Cross-sectional summary measure**
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 baseline cohort per person month (Variance)	Mean Incidence rate of clinical malaria in 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	Proportion HH with >=1 LLIN (First interview)	Proportion HH with >=1 LLIN
LLIN ownership	Proportion HH with >=1 LLIN per 2 residents (First interview)	Proportion HH with >=1 LLIN per 2 residents
Individual Characteristics		
Age	Mean age (SD)	Proportion under five
Sex	Proportion female	Proportion female
HH size	Mean hh size of participant's HH (SD)	Mean hh size of included hh (SD)
Net Use	Proportion Slept under net night before survey	Proportion (tested population) slept under net night before survey

Section 6: Analysis

Outcome definitions:

The primary outcome measure is the incidence rate of clinical malaria cases assessed among people aged 12 months to less than 15 years (≥5 to 15 in Mali). A clinical case is defined as an axillary temperature of ≥37.5° Celsius or self-reported fever within the past 48 hours, plus a positive malaria RDT. Incidence rate is defined as the total number of incident malaria cases divided by the total person-time observed among each cohort. Outcome assessment will be conducted on each cohort participant monthly. As malaria treatment drugs will be administered to all positive clinical cases (fever + positive RDT) after monthly case ascertainment, each positive participant will have two weeks of the following month of observation time subtracted from their at-risk person-time to account for the prophylactic effect of sustained antimalarial drug concentration and its potential to prevent reinfection. In individuals who have symptomatic indication for RDT testing at the month following a positive diagnosis of malaria via RDT and treatment, a positive RDT in the following month may only indicate persistence of antigen in the blood after effective treatment rather than true reinfection. In such cases PCR or microscopy results for a *P. falciparum* infection will be used to resolve if such infections are considered a result of persistent antigenemia or as a result of reinfection/recrudescence. In Mali, only microscopy will be used as resolver test. In Kenya and Zambia, PCR results will be used where available, and otherwise microscopy. Where the RDT and either the PCR or microscopy results are both positive in month two and the patient meets the other clinical criteria (patent fever or history of fever in the previous 48 hours) these observations will be treated as new clinical cases. To keep field procedures unambiguous, a blood slide will be taken whenever a positive RDT is recorded in Mali. Temporary absences from the study area not resulting in failure to ascertain monthly outcomes will not be considered as reducing individual exposure time. Absences greater than the testing interval (one month) and/or resulting in the failure to ascertain a monthly test result will be removed from the exposure time - meaning that exposure will only be considered to start one month prior to the most recent test result.

In summary:

- If a participant is symptomatic and positive by RDT they are treated and the subsequent two-weeks of follow-up time are censored
- If in the next month – the participant is also symptomatic and again positive by RDT – they will be treated and PCR or microscopy will be used to determine if they are considered a case of persistent antigenemia or a true new clinical case
- If PCR or microscopy in month two is positive, they are considered to have contributed the person-time between the previous visit and this visit less two weeks and they are considered to contribute a second case to the numerator, two more weeks of follow-up will be censored following the second positive.
- If PCR or microscopy is negative - then contributed follow-up time between last visit and this one less two weeks and only one case is included in the numerator and two more weeks of follow up time are censored after the second RDT positive (due to the required treatment).

Secondary outcomes:

1. Time to first infection

Time to first infection assessed among the cohort by PCR in Kenya and Zambia, and by microscopy with negatives confirmed by PCR in Mali. This indicator is calculated as the number of days from clearance confirmation until date of sample collection for first PCR positive test (or blood slide positive). Blood slide readings are confirmed by two independent, blinded readers with ties broken by a third (also blinded slide reader). All blood slide readers will be WHO certified level 1 malaria microscopists.

2. RDT infection prevalence

Prevalence of patent malaria infection detected by RDT among participants aged six months and older. Calculated as the number of eligible, consented participants with RDT collected during the cross-sectional survey with RDT positive results divided by the number of eligible, consented participants with valid RDT collected during the survey (or rolling in Kenya) cross-sectional survey.

3. Passive incidence

Incidence rate of passively reported clinical malaria among participants of all ages, defined as the number of malaria confirmed cases (by RDT or microscopy), linked to study clusters by place of residence, per 1,000 population per year, using routine data from health facilities with patients linked to study clusters (*i.e.* by name of village of residence) and cluster population sizes for the denominator. Cluster population sizes will be calculated based on the number of HH residents identified in the cluster area (core only where possible/relevant) during the census/enumeration. Malaria confirmed cases will include only those given a diagnosis of blood test (RDT or microscopy) confirmed malaria (ICD-10-M B50-54 and subcodes).

Analysis methods

Primary outcome:

The primary unadjusted analysis will be conducted on the intention to treat analysis population without adjustment for any anticipated confounding variables as these are considered to be balanced due to randomization. The analysis of the primary outcome, cumulative clinical incidence of malaria, will be analyzed using a multi-level (variance compartments model) 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 will be included as a fixed effect coded categorically as 0 for arm A and 1 for arm B. The analyst will be blinded to the true assignment until the allocation code is broken. The model will take the form below where y_{ij} is incidence at the individual (*i* indexes individuals within clusters and *j* indexes clusters), alpha is the global intercept, X_{ij} is the arm assignment for individual *i* in cluster *j*, B_{arm} is the arm effect to be estimated, u_j are random intercepts for the cluster and $exposure_{ij}$ is the person time at risk for individual *i* in cluster *j*, *lambda* refers to the $log\ E(y_{ij}|u_j)$ and *sigma* is the standard deviation of the random intercept distribution:

$$\log E\left(y_{ij}\middle|u_j\right) = \alpha + X_{ij}^{arm}\beta_{arm} + u_j + \log\left(exposure_{ij}\right)$$

Where the likelihood is of the form:

$$y_{ij} \sim Pois(\lambda)$$

And the random intercepts are assumed to follow a normal distribution:

$$u_j \sim N(0, \sigma^2)$$

Results will be presented as the incidence rate ratio (IRR), corresponding 95% confidence interval and p-value based on the z-statistic. 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 variance is substantially larger a negative binomial likelihood will be considered.

Covariate adjusted analysis of the primary and secondary outcomes:

Adjusted analyses will be carried out on the analysis of the primary and secondary outcomes to determine whether the estimate of treatment-effect is affected with the inclusion of additional covariables. The prespecified covariates will be developed and tested prior to final analysis but specific to each site. For the primary and secondary outcomes, one additional analysis will include all covariables which are used in restricted randomization with variables treated exactly as specified in randomization. Because these variables cannot be fully prespecified until the restricted randomization is complete, the full specification of these covariables cannot yet be made. However, these analyses will be prespecified for the primary outcome prior to data lock and the statistical analysis plan for each trial site will be updated to reflect these analyses. Examples of prespecified covariates that may be included in the adjusted analyses are described in table 6 which will be finalized prior to data lock.

Table 6: Proposed Covariables

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

Subgroup analysis of the primary outcome

We will perform a series of subgroup analyses according to the list subgroups in the table below. Imputation for these baseline missing covariates (see section *Missing Data*) will be carried out before categorizing. Assessment of the homogeneity of treatment effect by a subgroup variable will be conducted by inclusion of the treatment, subgroup variable, and their interaction term as predictors in the adjusted models of primary outcome, and the *p*-value presented for the interaction term. If the p-value is less than 0.05, we will present separate effect estimates and CIs for each category of the subgroup variable.

Table 7: Planned Sub group analyses

Subgroup Name	**Categorization**	**Rationale**
Housing type	Closed eaves vs. Non-closed eaves	House structure may act as effect modifier by eliminating indoor biting risk independent of ATSB deployment
Gender	Male vs. Female	Behavioral and occupational difference may act as effect modifier; to demonstrate equity of the intervention effect
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 impact of ATSB by increasing environmental carrying capacity for 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 lower incidence	(Kenya only)
Age	<= 60 months of age vs > 60 months of age	Behavioral differences by age may act as effect modifier
Baseline Prevalence	High vs. low (>= median cluster prevalence vs. < median cluster prevalence)	Local endemicity may act as an effect modifier

Secondary outcomes:

Time to first infection:

Time to first infection assessed among the cohort by PCR in Kenya and Zambia, and by microscopy with negatives confirmed by PCR in Mali. Time to first infection will be analyzed using a Cox-proportional Hazards model with a shared frailty for study cluster and a 'fixed' effect coefficient for arm will be included as a fixed effect coded categorically as 0 for arm A and 1 for arm B. The analyst will be blinded to the true assignment until the results are presented. The model takes the form below where h_{ij} is hazard at the individual (*i* indexes individuals within clusters and *j* indexes clusters), $h_0(t)$ is the underlying cumulative hazard, X_{ij} is the arm

assignment for individual *i* in cluster *j*, B_{arm} is arm effect, u_j are shared frailties for the cluster and *k* and *theta* are parameters of the shared frailty distribution, where k is constrained to be equal to one.

$$h_{ij}(t) = u_j h_0(t)\, exp(\, B_{arm} X_{ij}^{arm})$$

Where the shared frailties are assumed to follow a gamma distribution.

$$u_j \sim \Gamma(k = 1, \theta)$$

Model results will be presented as the estimates of the hazard ratio and *theta* parameters of the frailty distribution. 95% confidence intervals for the hazard ratio as well as z-statistics and p-values for each coefficient will be presented.

The proportional hazards assumption will be checked for the effect of arm, will be testing 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.

Prevalence outcomes:

Prevalence of malaria infection among participants aged six months and older, detected by RDT will be analyzed using a multi-level (variance components model) constructed on a generalized linear model framework with a bernoulli likelihood and a logit link function. Random intercepts will be included for each study cluster and study arm will be included as a fixed effect coded categorically as 0 for arm A and 1 for arm B. The analyst will be blinded to the true assignment until the results are presented. The model will take the form below where p_{ij} is probability of positivity at the individual level (*i* indexes individuals within clusters and *j* indexes clusters), alpha is the global intercept, X_{ij} is the arm assignment for individual *i* in cluster *j*, B_{arm} is the arm effect to be estimated, u_j are random intercepts for the cluster and *sigma* is the standard deviation of the random intercept distribution:

$$\text{logit}(p_{ij}) = \alpha + X_{ij}^{arm}\beta_{arm} + u_j$$

Where the likelihood is of the form:

$$y_{ij} \sim bernoulli(\, p_{ij})$$

And the random intercepts are assumed to follow a normal distribution:

$$u_j \sim N(0, \sigma^2)$$

Model results will be presented as the estimates of alpha and the odds ratio above and the standard deviation or variance of the random effects distribution. 95% confidence intervals for the odds ratio and alpha estimates as well as z statistics and p-values for each coefficient will be presented.

Routine Clinical Incidence:

The incidence of clinical malaria obtained from passive case detection, will be analyzed as monthly incidence using a multi-level (variance compartments model) 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 will be included as a fixed effect coded categorically as 0 for arm A and 1 for arm B. Month will be include as a categorical (fixed effect and dummy coded) and exposure will be the population of the cluster as assessed during enumeration. The analyst will be blinded to the true assignment until the results are presented. The model will take the form below where y_{ij} is monthly incidence at the cluster level where only aggregated data is available (*i* indexes clusters and *month* indexes months), alpha is the global intercept, X_{ij} is the arm assignment for cluster *i*, B_{arm} is the arm effect to be estimated, XB_{month} represent a series of dummy variables for month of the year and their associated effects$_j$ $exposure_{ij}$ is the person time at risk for *month* in cluster *i*, *lambda* refers to the *log* $E(y_{ij}|u_j)$ and *sigma* is the standard deviation of the random intercept distribution:

$$\log E\left(y_{i,month}\middle|u_i\right) = \alpha + X_{i,month}B_{arm} + \sum_{month} X'_{i,month}\beta_{month} + u_i + \log\left(,month\right)$$

Where the likelihood is of the form:

$$y_{i,month} \sim Pois(\lambda)$$

And the random intercepts are assumed to follow a normal distribution:

$$u_i \sim N(0, \sigma^2)$$

Model results will be presented as the estimates of alpha and Incidence Rate Ratios above and the sd or variance of the random effects distribution. 95% confidence intervals for the IRR and alpha estimates as well as z statistics and p-values for each coefficient will be presented, and the overall model AIC estimate will also be presented. Results will be presented as incidence rates and incidence rate ratios along with their associated 95% confidence intervals, and *p*-values.

The outcome will also be checked for 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 variance is substantially larger a negative binomial likelihood will be considered.

Where individual level data is available for this outcome a similar approach will be followed but instead focused on cumulative incidence. The model will take the form below where y_{ij} is incidence at the individual (*i* indexes individuals within clusters and *j* indexes clusters), alpha is the global intercept, X_{ij} is the arm assignment for individual *i* in cluster *j*, B_{arm} is the arm effect to be estimated, u_j are random intercepts for the cluster and $exposure_{ij}$ is the person time at risk for individual *i* in cluster *j*, *lambda* refers to the *log* $E(y_{ij}|u_j)$ and *sigma* is the standard deviation of the random intercept distribution:

$$\log E\left(y_{ij}\middle|u_j\right) = \alpha + X_{ij}^{arm}\beta_{arm} + u_j + \log\left(exposure_{ij}\right)$$

Where the likelihood is of the form:

$$y_{ij} \sim Pois(\lambda)$$

And the random intercepts are assumed to follow a normal distribution:

$$u_j \sim N(0, \sigma^2)$$

Results will be presented as the incidence rate ratio (IRR), corresponding 95% confidence interval and p-value based on the z-statistic. 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 variance is substantially larger a negative binomial likelihood will be considered.

Additional Analyses

Individual Pooled Analysis across sites

Individual pooled analysis across the three trial sites (countries) will be conducted collectively following completion of all three trials. This analysis will follow similar statistical principles to each analysis specified above. Additionally, a standard individual patient data meta-analysis is expected to be conducted using combined data from all sites.

Missing data

Missing outcome data

Significant effort will be made to reduce missing outcome data by revisiting cohort house-holds 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. Missing outcomes due to participant absence will result in censoring (removal of the previous period of follow up time if there is a missing outcome). Participants who return to 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. They will also have two weeks of the next period follow up time removed as per definition of the primary outcome. Two sensitivity analyses will be carried out for the primary outcome. These will be last observation carried forward (***e.g.*** an assumption that a clinical malaria case identified at the last time point observed would represent subsequent new clinical cases (and follow up time removal) at each missing time point or that the absence of a clinical case at last observation would indicate no clinical cases observed at any missing time points and full follow up time) this analysis is consistent with a true intention to treat protocol. Since a true ITT analysis requires no LTFU and therefore requires some form of imputation when LTFU occurs. The second sensitivity analysis will be to assume that all missing values would have resulted in negative findings thus imputing zero extra unobserved clinical cases across both study arms and assuming full follow up time. These analyses will only be applied to the intention to treat analysis population because the per-protocol study population already assumes that full follow up (all outcome assessments) occurred. Full reporting of the fraction of missing outcome assessments by study arm will be conducted for the intention to treat study population.

Missing co-variates

Missing baseline covariates (as defined in the SAP prior to data lock) will be imputed using simple imputation methods in the covariate adjusted analysis based on the covariate distributions, should the missing values for a particular covariate 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 P_1, P_2, … P_k from the sample. Seed for the imputation will be preset as an 8-digit number based on the date of analysis and documented in all scripts relying on pseudo-random number generators. If the missing values for a covariate are ≥5% then they will be imputed using Markov chain Monte Carlo (MCMC) methods (van Buuren *et al* 2006).

Harms

The main risks associated with the intervention are the risk of ingestion of the bait by humans, animals, and/or non-target arthropods – particularly the local bee population. As the main harms are not expected to be encountered by study participants there is no formal plan for statistical analyses of harms to study participants. Continued entomological monitoring of non-target insect populations and ongoing monitoring of trial sites for misuse or product loss will be conducted and these data will be reviewed by the DSMB but they will not be formally analyzed statistically. Unexpected harms may occur during the course of trial and will be considered in reviews and by DSMB though no formal analysis is planned.

Statistical software

Statistical software and hardware platforms may will vary by trial site. Reporting of statistical analysis will include specific details of software platform, including language, version and details of any additional libraries used in analysis.

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