Repeat Ivermectin Mass Drug Administrations for MALaria Control II (RIMDAMAL II): a double-blind, cluster-randomized control trial for integrated control of malaria.

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LIST OF ABBREVIATIONS

ACD	Active Case Detection
AE	Adverse Event/Adverse Experience
AL	Artemether-lumefantrine
ALT	Alanine Aminotransferase
AQ	Amodiaquine
ASAQ	Artesunate-Amodiaquine
AST	Aspartate Aminotransferase
BLA	Biologics License Applications
CAR	Clinical Agents Repository
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
Cr	Creatinine
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DOT	Directly Observed Therapy

DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIC	Human Investigations Committee
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRSS	Institute de Recherche en Sciences de la Santé
IVM	Ivermectin
IPTp	Intermittent Preventative Treatment in Pregnancy
JAMA	Journal of the American Medical Association
LLIN	Long-lasting Insecticide-Treated Bed Net
MDA	Mass Drug Administration
MedDRA®	Medical Dictionary for Regulatory Activities

mFOI	Molecular Force of Infection
MoH	Ministry of Health
MOI	Multiplicity of Infection
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NDOT	Non-directly Observed Therapy
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
NMCP	National Malaria Control Program
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PD	Pharmacodynamics
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Seasonal Malaria Chemoprevention
SOC	Safety Oversight Committee
SOP	Standard Operating Procedure
SPAQ	Sulfadoxine-Pyrimethamine-Amodiaquine

US	United States
WHO	World Health Organization

PROTOCOL SUMMARY

Title:	Repeat Ivermectin Mass Drug Administrations for MALaria Control II (RIMDAMAL II): a double-blind, cluster-randomized control trial for integrated control of malaria.
Phase:	3
Population:	14 villages, 2 arms (7 clusters/arm); all heathy and eligible participants (both genders and all ages), approximately 4,700 people who live in southwestern Burkina Faso
Number of Sites:	1 site in southwestern Burkina Faso
Study Duration:	3 years (between 2018-2021)
Subject Participation Duration:	2.5 years (2019-2021)
Description of Agent or Intervention:	generic ivermectin, 6 mg tablet; dose: 3-day oral regimen of 300 µg/kg/day estimated by height bands, administered monthly for 4 months/rainy season over 2 consecutive rainy seasons.
Objectives:	Primary: • To assess the impact of a combined approach of repeated IVM MDA and SMC on malaria incidence in children, with the purpose of testing the superiority of IVM compared to placebo for reducing malaria incidence. Our hypothesis that IVM MDAs (the intervention), coinciding with standard of care antimalarial procedures in Burkina Faso (four SMC rounds during the rainy season, maximum LLIN coverage and IPTp for pregnant women), will significantly reduce the incidence of childhood malaria in the intervention arm compared to the control arm. The IVM MDAs will consist of generic IVM or IVM placebo (e.g. Iver P®, Elea Labs; 6 mg tablet) given monthly

from July-October (4X) as a 3-day course to all eligible persons who meet inclusion criteria (≥90 cm and not treated with SMC (≥ 5 years), not pregnant or breast feeding an infant less than 1 week old). Dosing of IVM or placebo will be according to height as indicated on the package: 90-119 cm = 1 tablet/day for 3 days; 120-140 cm = 2 tablets/day for 3 days; 141-158 cm = 3 tablets/day for 3 days; >158 cm = 4 tablet/day for 3 days.

Secondary:

- To measure whether the IVM MDAs will increase harms in the participants
- To measure the entomological indices (mosquito survival rate after blood feeding, mosquito population age structure, sporozoite rate if they are infected with *Plasmodium* parasites, human exposure to *Anopheles* mosquito bites) between the intervention and control arm and over the time of the intervention phase.
- To measure the parasitological indices obtained from blood samples collected during the active case surveillance of cohort children, between the intervention and control arms and over the time of the intervention phase. These indices are asexual parasite prevalence, species, density, the multiplicity of infection, and the molecular force of infection (mFOI).
- To link the pharmacokinetics-dynamics of ivermectin in a sub-cohort of the treated study population to mosquito blood feeding and survival.

Exploratory:

- NA

Outcome Measures:

Primary:

- The incidence of malaria episodes in cohort children ≤10 years of age as assessed by active case surveillance. Malaria incidence in children is the most clinically-relevant outcome measure in this field setting from an anti-vector intervention that targets blood feeding mosquitoes, and its reduction following repeated IVM has been validated from our prior RIMDAMAL I study. Study nurses will visit each child weekly to monitor for malaria episodes. At each visit, a temperature reading will be recorded. If the axillary temperature is ≥37·5°C (or analogous temperature from another site) and/or history of fever in the last 24 hours, a blood sample will be taken and assessed by rapid diagnostic test (RDT) for *Plasmodium* spp. If this is also positive, this will be considered a positive malaria episode.

Secondary:

- AE monitoring will occur both actively and passively. All AE will be graded and analyzed by seriousness, intensity and causality. AE monitoring in this study is crucial to properly weigh the potential benefits vs. potential risks of the study.

  In the entire enrolled populace, passive monitoring of AEs will occur through spontaneous reporting of adverse events to the study clinical team and recorded on CRFs. Active monitoring of AEs will occur among participants in two ways, a) on the days of distribution of ivermectin/placebo through direct questioning of participants for AEs and recording on CRFs by study nurses and, b) in a weekly visit and assessment of participants living in selected households located on our entomological sampling transects. AEs will be recorded from the entire enrolled populace, regardless if they were treated with ivermectin/placebo or not eligible to take the intervention. AE will be recorded over the intervention period occurring during the 1st and 2nd rainy seasons. More

specifically, AEs will be recorded from the start of the first MDA of each rainy season to 1 month after the last MDA of that season.

For those children enrolled in the active case detection cohort, where children are visited weekly to assess for malaria incidence, active monitoring of AEs will occur through direct questioning of AEs by the study team. Additionally, passive monitoring of AEs will occur by participants spontaneously reporting directly to the nurses when the nurses are in the villages performing active case detection of malaria in the child cohort, or spontaneously reporting indirectly to the nurses via communication through the village community health worker (who will then communicate the AE directly to the nurse or field physician).

For women that become pregnant during the intervention period, monitoring for birth outcomes will be conducted.

- Entomological indices will provide a first-order mechanistic explanation of the intervention's effect on malaria incidence (the primary outcome): Wild, blood-fed, indoor-aspirated, *Anopheles* will be held in cages and scored for survival rates over time, which will be analyzed across arms. The age structure of captured *Anopheles* will be analyzed over time and analyzed across arms. Captured wild mosquitoes will be dissected and analyzed for sporozoite infection rates over time and analyzed across arms. A cohort of participants' sera immuno-reactivity to an *Anopheles* saliva antigen will be analyzed over the intervention period of each season.
- Parasitological indices will provide a second-order mechanistic explanation of the intervention's effect on malaria incidence (the primary outcome): Prevalence, species and densities of asexual parasitemias will be scored from stain blood smears and analyzed over time and across arms, in both blood samples taken during the active case surveillance of cohort children, and in cross-sectional

sampling of the whole study population. The genetic markers of parasites in participant dried blood spots will be analyzed for the multiplicity of infection, and the molecular force of infection over time.

- Pharmacokinetics-dynamics will be studied in a sub-cohort of participants to link the presence of drug with mosquito biting and survival: Ivermectin in blood samples from different treated subjects (different age strata and genders) will be quantified and used to construct models to estimate and compare the pharmacokinetic parameters (e.g. C_{max}, $T_{1/2}$) across strata in blood. Entomology sampling in the houses of these participants following treatment will collect blood fed mosquitoes that will be 1) analyzed for survival, 2) tested for ivermectin in their blood meals, and 3) for the genetic signatures of the studied participants in the blood meal.

Description of Study Design:

A cluster-randomized control trial will be conducted in a single region of southwestern Burkina Faso over two consecutive rainy seasons and designed to integrate repeated high-dose IVM MDA (the intervention) into the regular, monthly SMC delivery platform and with other existing malaria control methods conducted in the villages. Fourteen villages (clusters) in the region will be recruited to participate in this double-blind, parallel-assignment trial with two arms randomized in a 1:1 ratio (Table 1; Figure 1). The intervention (IVM MDA) is predicted to primarily reduce the survival of biting *Anopheles* mosquito vectors, which will reduce *Plasmodium* transmission. Since children suffer a high burden of malaria due to the inadequate immunity they have developed against repeated *Plasmodium* infections, reduced *Plasmodium* transmission is expected to reduce malaria incidence in the child cohort. The hypothesis is that IVM MDAs coinciding with SMC rounds will significantly reduce the incidence of malaria in children compared to the standard malaria control interventions currently

conducted (four SMC rounds to 3-59 month old children, high LLIN coverage, and IPTp). The two arms will specifically receive:

- Standard of care:
    - Active LLIN distribution in the villages will be maintained by the MoH.
    - SMC given monthly from July-October (4X) with SP+AQ (e.g. SPAQ-CO™, Guilin Pharmaceutical; 500/25 mg S/P and 153 mg AQ for children 12-59 months; 250/12.5 mg S/P and 76.5 mg AQ for children 3-11 months. SMC will be provided by the Burkina Faso MoH
    - IPTp provided to all pregnant women with SP by the Burkina Faso MoH. WHO and Burkina Faso MoH policy recommends at least 3 treatments, 1 month apart, starting in second trimester. Provided by the Burkina Faso MoH (e.g. Fansidar®, Roche; 500/25 mg S/P per tablet, 3 tablet dosage (1500/75 mg S/P)).
- Study intervention:
    - Generic IVM or placebo (6 mg tablet) given monthly from July-October (4X) as a 3-day course to all eligible persons per exclusion/inclusion criteria. Per package insert, dosing of IVM or placebo will be according to height to approximate weight: 90-119 cm (15-25 kg) = 1 tablet/day for 3 days; 120-140 cm (26-44 kg) = 2 tablets/day for 3 days; 141-158 cm (45-64 kg) = 3 tablets/day for 3 days; >158 cm (65-84 kg) = 4 tablet/day for 3 days.

Village population size is expected average approximately 360 people, and all eligible persons in each village will be asked to enroll, thus giving us an enrolled population of approximately 5000 participants. These will be otherwise healthy individuals who live in a hyperendemic malaria region. Our primary outcome is the incidence of malaria

episodes in children ≤ 10 years of age over two rainy seasons. The sample size is based on a mathematical modeling of this outcome and suggests we should observe an effect size in the intervention arm over the control arm of 43.1%, assuming a rate incidence in our ≤10 yr. old cohort of 1.088 malaria episodes/child/year and 0.619 malaria episodes/child/year in the control and intervention arms, respectively, in the presence of standard LLINs. The primary outcome will be analyzed as intention-to-treat. Safety of IVM will be assessed as a secondary outcome to ensure the intervention does not increase harms to the populace, and entomological, parasitological, and pharmacokinetic-dynamic parameters also assessed as secondary outcomes to provide an understanding of the basis of IVM's impact in the context of this trial.

Estimated Time to Complete Enrollment:

1 year.

Table : Treatment Arms

Arms	Participant population	Intervention
Arm 1	7 villages; ~2500 participants • ~75% will receive the placebo MDA intervention (all eligible persons ≥90 cm not taking SMC (≥ 5 years) or pregnant or breast feeding an infant < 1 week old). • >700 cohort children ≤10 yrs. of age (~10-children/cluster) followed by active case detection for malaria	standard of care plus placebo MDA
Arm 2	7 villages; ~2500 participants • ~75% will receive the ivermectin MDA intervention (all eligible persons ≥90 cm not taking SMC (≥ 5 years) or pregnant or breast feeding an infant < 1 week old). • >700 cohort children ≤10 yrs. of age (~100 children/cluster) followed by active case detection for malaria	standard of care plus ivermectin MDA

Figure 1: Schematic of Study Design

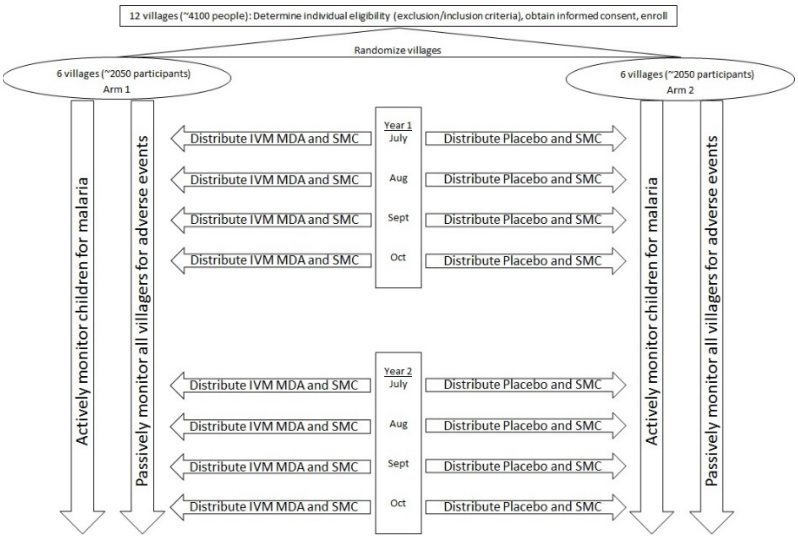
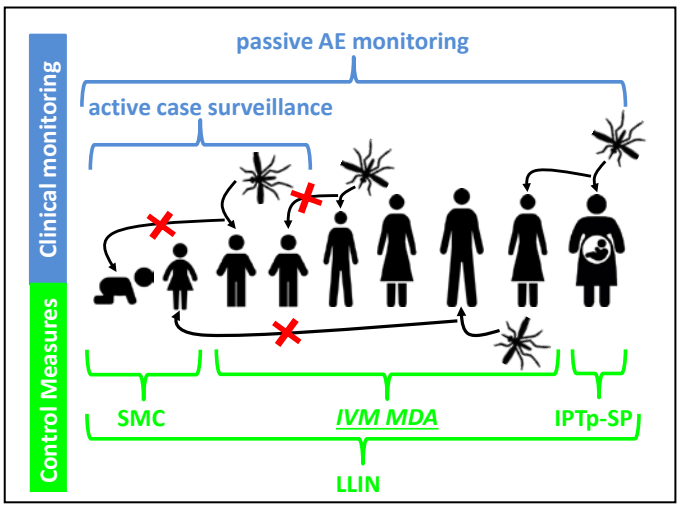


Figure 2: Study Graphic



1. KEY ROLES

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2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

Ivermectin (IVM) is the drug to be used in the intervention. It is a semi-synthetic avermectin derivative that was first licensed in 1981 as a veterinary drug. It has a broad spectrum of activity against parasitic nematodes and ectoparasites, high potency, and a relatively long pharmacokinetic persistence in blood and lymph. The drug is a macrocyclic lactone that targets invertebrate-specific ligand gated ion channels, hyperpolarizing their neurons, and causing them flaccid paralysis and death (1). In 1987, IVM was first approved for human-use to control onchoceriasis. Studies on its activity against mosquitoes began in the early 1980's, where it was soon discovered that *Anopheles* species were highly sensitive to serum drug levels achieved from standard doses to persons as an anthelmintic. Since then, many reports have shown its ability to kill and impair *Anopheles* vectors when they ingest blood either directly or indirectly from treated humans and animals (Table 2).

Table 1: Efficacy of ivermectin against *Anopheles* vectors

Publication	**Method and Dose**	***Anopheles* species**	**Results**
Iakubovich, 1989 (2)	Membrane and feeding on treated rabbits. Dose: 340 µg/kg (once, subcutaneous)	*An. stephensi*	Death rates among *An. stephensi* fed on rabbits 4, 5 and 6 days after administration of the drug were 93, 70 and 79%, respectively.
Gardner, 1993 (3)	Feeding on treated dogs Dose: 6–24 µg/kg (once, orally)	*An. quadrimaculatus*	Significant increase in mortality. LD50= 9.9 µg/kg [6.0, 13.8]

			Significant decrease in oviposition and egg-hatching from survivors
Bockarie, 1999 (4)	Field collections of engorged wild mosquitoes before and after MDA for LF Dose: 400 µg/kg ivermectin +/- 6 mg/kg DEC (once, orally)	*An. punctulatus* *An. koliensis*	Significant decrease in 9-day cumulative survival rate of *Anopheles* spp. collected 1–3 days post-treatment (0%) vs those collected pre-treatment (67%) The 48-hr survival rate of *An. puctulatus* collected from two houses in the a treated village the morning following MDA was 31% vs 94% from two houses of an untreated village
Foley, 2000 (5)	Feeding on one treated human volunteer Dose: 250 µg/kg (once, orally)	*An. farauti*	12-day cumulative mortality rate of mosquitoes was 100%, 95%, 93%, and 40% for those fed 0, 7, 10 and 14 days post-treatment vs 10% for those fed pre-treatment
Fritz, 2009 (6)	Membrane and feeding on treated cattle	*An. gambiae*	Membrane feeding: LC50 for *An. gambiae*

	Dose: 600 µg/kg (once, subcutaneously)	*An. arabiensis*	s.l. was 19.8 ± 2.8 ppb; no oviposition from mosquitoes fed on >10 ppb Cattle feeding: Total cumulative survival of *An. gambiae* s.s. significantly different from controls when fed up to 20 days post-treatment; no or significantly reduced oviposition when fed up to 17 days post-treatment
Chaccour, 2010 (7)	Feeding on randomized, treated volunteers and controls Dose: 200 µg/kg (once, orally)	*An. gambiae*	Mean 12-day survival time of 2.38 days [1.52, 3.24] for mosquitoes fed on treated subjects at 1 day post-treatment vs 5.52 days [4.65, 6.4] for mosquitoes fed on untreated control Subjects No effect on mosquitoes fed on treated subjects at 14 days post-treatment

*Kobylinski, 2010 (8)	membrane feedings Dose: NA	*An. gambiae*	LC50 = 22.4 ng/ml [18.0, 26.9]. At sub-lethal concentrations, significantly reduced mosquito re-blood feeding rates and a second ivermectin blood meal, even at a decreased concentration, further increased mortality
*Sylla, 2010 (9)	Field collections of engorged wild mosquitoes before and after MDA for onchocerciasis Dose: 150 µg/kg ivermectin (once, orally)	*An. gambiae* *An. arabiensis*	5-day cumulative survival of *An. gambiae* s.s. was significantly reduced from 3 treated villages vs pair-matched control villages
*Butters, 2012 (10)	Membrane feeding Dose: NA	*An. gambiae*	Sub-lethal concentrations (LC25 & LC5) caused significant knockdown and reduced recovery rates
Fritz, 2012 (11)	Membrane feeding Dose: NA	*An. arabiensis*	LC50 = 7.9 ppb [6.2, 9.9]; oviposition among survivors was significantly reduced at ≥7 ppb
Bastiaens, 2012	Feeding on treated Swiss mice, Wistar rats	*An. stephensi*	3-day cumulative mortality of

	and Cynomolgus monkeys Dose: 200–400 µg/kg (different intervals, orally)		mosquitoes fed on treated mice, rats and monkeys significantly differed from controls when fed up to 2, 4 and 3 days post-treatment, respectively
*Kobylinski, 2012 (12)	Membrane feeding Dose: NA	*An. gambiae*	Sub-lethal concentrations significantly inhibited *P. falciparum* sporogony when fed prior to, concurrent with, and 6 and 9 days after infection with gametocytes
*Alout, 2014 (13)	Field collections of engorged wild mosquitoes before and after MDA for LF or onchocerciasis Dose: 150 µg/kg ivermectin, +/- 400 mg albendazole (once, orally)	*An. gambiae*	*An. gambiae* s.l. captured in treated villages 1–6 days post-treatment had significantly reduced survival vs. those caught pre-MDA and those caught >7 days post-treatment
* denotes publications from members of the study team LC5, LC25, LC50; the lethal concentrations calculated to kill 5%, 25% and 50% of treated mosquitoes. (adapted from Chaccour *et al*, 2013 Malaria J.)			

In the two decades following the initial studies demonstrating the efficacy of ivermectin for killing mosquitoes, the concept was mostly limited to ideas centered on total control of a vector population from treating individual hosts and testing direct mortality effects against vectors that ingested the drugs in host blood meals. Over the last 8 years, these ideas around malaria vector control were refined, and experiments were undertaken to test whether MDA of ivermectin in West African villages for onchocerciasis and/or lymphatic filariasis (LF) control, when applied during malaria transmission seasons, could significantly reduce the vectorial capacity of vectors biting the community (13). The effects have been strong and consistent. Single MDAs of 150 µg/kg and achieving ≥ 75% drug coverage of the village population reduced the daily probability of *A. gambiae* s.l. (indoor-resting, blood fed mosquitoes) survival by ~11% for approximately one week. This mortality effect results in ~25% reduction in parity rate of mosquitoes collected host-seeking outdoors for approximately 2 weeks, which demonstrates that the age structure of the vector population significantly shifts to younger age classes around the village. As young mosquitoes have not lived long enough to become infectious, this results in at least a ≥78% reduction in vectorial capacity, and significant reductions (>77%) in sporozoite rates for two weeks following the MDA (9, 14). While very transient, these reductions are in-line with changes seen in *A. gambiae* populations around SSA villages when IRS has been implemented (15) or LLINs distributed (16).

There are several ways to achieve a longer lasting mosquitocidal effect so that malaria transmission control might be sustained over limited malaria transmission seasons, like occur in the countries of the African Sahel. Using currently-approved IVM drug formulations and doses, the dose could be increased up to 400 µg/kg, such as is approved for lymphatic filariasis and scabies control in some regions, and/or given repeatedly. New IVM formulations might also be eventually developed that produced longer pharmacokinetic-dynamic profile in the blood of treated individuals, however this will require a long period of time for development and safety testing.

Frequent, repeat IVM treatment is necessary and has been used for cases of persistent helminthiasis, and for hyper-encrusted scabies patients (17, 18). A number of older trials have reported on the efficacy and safety of frequently repeated IVM treatment in small groups of healthy or helminth-infected individuals. These are summarized in Table 3.

Table 2: Studies reporting frequent, repeated ivermectin administrations and their safety.

Publication or Trial	Patient Populations	Dose	Frequency	Safety Outcome
Duke, 1990 (19)	36 *O. volvulis*-infected Guatamalan patients	150 µg/kg	every month for either 4, 8 or 12 months	No AEs/SAEs reported
Duke, 1991 (20)	30 *O. volvulis*-infected Liberian patients	~100 µg/kg	every 2 weeks for 10 weeks	No AEs/SAEs reported
Duke, 1992 (21)	36 *O. volvulis*-infected Guatamalan patients	150 µg/kg	every 3 months for either 9, 12 or 31 months	No AEs/SAEs reported
Ismail, 1996 (22)	14 *W. bancrofti*-infected Sri Lankan patients	400 µg/kg	11 doses every 2 weeks	Mild AEs in 13 subjects but only after the first dose – suggestive of a link to microfilaria death and clearance; localized inguinal/scrotal reactions linked to a macrofilaricidal effect.
Awadzi, 1999 (23)	85 *O. volvulis*-infected Ghanian patients	150-800 µg/kg, then 400-800 µg/kg	2 doses, administered on days 1 and 4	No AEs/SAEs reported
Kamgno, 2004 (24)	155 *O. volvulis*-infected	150 µg/kg	every 3 months for 3	Significantly *fewer* AEs relative to groups

& Gardon, 2002 (25)	Cameroonian patients		years (12 doses)	receiving one dose annually, including fewer sundry pains, back/wrist pain, headache, fever, pruritis, & oedematous swellings. No SAEs reported.
Guzzo, 2002 (26)	15 healthy American patients	347-594 µg/kg	3 times over 1 week	AEs similar between IVM and placebo and did not increase with dose. No SAEs reported; CNS toxicity not detected.

Overall, these studies demonstrated that frequent and repeated IVM treatment were well-tolerated and induce few or no AE/SAEs in the patients. More recently-completed clinical trials have validated repeated and higher dose IVM's effect against malaria vectors (two of these paired the IVM treated with antimalarials), the safety of these treatments, and their efficacy in reducing disease.

The individually-randomized, double-blind, placebo-controlled ACTIVE trial (NCT0160325) was conducted in Burkina Faso in 2013, and examined the safety and mosquitocidal efficacy of a treatment regimen for asymptomatic *P. falciparum*-infected individuals aged 15-25 years, consisting of a regular artemether-lumefantrine (AL) course plus 200 µg/kg IVM given with the first AL dose (AL-IVM1) or first and fifth AL dose (AL-IVM2) compared to AL plus placebo (27). The trial showed that both AL-IVM treatments were well-tolerated and cleared asexual parasites equal to the control. Furthermore, *Anopheles gambiae* survivorship over 10 days after membrane-feeding on participants' blood 3 days post-treatment was ~75% in the control arm, ~65% in the AL-IVM1 arm, and ~30% in the AL-IVM2 arm, suggesting a 27% and 35% reduction, respectively, in the estimated malaria transmission during the first week after treatment.

IVERMAL (NCT02511353) was a similarly-conducted, individually-randomized, double-blind, placebo-controlled trial conducted in Kenya in 2015, which examined the safety and mosquitocidal efficacy of a treatment regimen for symptomatic *P. falciparum*-infected individuals aged 15-50 years (28). The treatment arms consisted of a regular dihydroartemisinin-piperaquine (DP) course (320/40 mg once a day for 3 days) plus placebo or IVM at 300 µg/kg/day or 600 µg/kg/day on the same 3 days. The investigators showed that the DP plus IVM 300 µg/kg/day regimen did not increase harms to the

participants, and the mosquitocidal effect from participants' blood lasted nearly *1 month* post treatment compared to placebo controls.

Our own team conducted a pilot, phase 2/3 cluster-randomized clinical trial on the safety and efficacy of repeated IVM MDA in Burkina Faso (RIMDAMAL trial; NCT02509481) in 2015. We enrolled 8 villages (2712 participants) and administered 6 rounds IVM MDA to 4 randomized intervention arm villages, every 3 weeks, from late July through late November (control arm villages received only the first IVM MDA, as per standard policy for LF elimination ongoing at the study site). IVM, as per label guidelines, was only administered to individuals whose height was ≥90cm. Our primary outcome was cumulative incidence of clinical malaria episodes in children ≤5 years of age. Active surveillance by trained nurses was performed 3 times every 2 weeks, and rapid diagnostic test (RDT)-positive malaria episodes were immediately treated with AL. The results showed that approximately 500 cases of malaria were averted per 1000 intervention arm children over the 18 week study (malaria incidence intervention arm=2.00, control arm=2.49, risk ratio=0.80 [0.70-0.91], P=0.0009). The safety outcome from this trial was the number and type of adverse events (AE) recorded in the enrolled populace (2712 participants). The risk of AE was not noticeably different among participants of the intervention arm (3.1% of participants [45/1447]) vs. the control arm (1.9% of participants [24/1265]); risk ratio = 1.63 [1.01-2.67], P = 0.06. Most AE (85%; 55/65) were classified as "not related" to the intervention, while 5 were classified as "unlikely related", 1 as "possibly related", 7 as "probably related", and 1 was unclassified. Of the "possibly" and "probably" intervention-related AE, all were sub-classified as adverse reactions of mild or moderate intensity that consisted of vomiting, pruritus, edema in the limbs, or tremors, and all were monitored until resolved or given standard treatment as outlined by WHO guidelines(29). 20 deaths were recorded over the study period, all classified as either "unlikely" or "not related" to the intervention. The risk of AE between arms among all participants was similar, as was the risk of AE among the child cohort. The proportions of each sub-class of AE, the graded intensity category, or the outcomes did not differ between the arms. In total, these data suggest that administering repeated IVM to entire villages does not increase harms in the populace.

2.2. Rationale

Malaria is a major cause of morbidity and mortality in Burkina Faso; it has some of the highest transmission intensities in the world, as assessed by the entomological inoculation rate (http://www.map.ox.ac.uk/), and there has been limited decrease in endemicity of the disease that has been observed in other SSA countries (30). The most prevalent species of parasite is *Plasmodium falciparum*, with less than 20% being *Plasmodium malariae* or *P. ovale* (31). A high proportion of persons living in rural, underdeveloped villages in endemic areas are infected with the malaria parasites throughout the year, but transmission is highly seasonal, beginning with the onset of the rainy season

and a subsequent dramatic increase of the malaria vector population (32). As such, the burden of overt clinical disease is on children ≤ 5 years of age who have not developed adequate immunity. In the southwest, clinical incidence is between 2-4 episodes per child per year (33). Clinical incidence in this age stratum spikes at the onset of the rainy season, likely due to a sharp increase in transmission events of new parasite clones accompanying the rise in mosquito populations at the start of rains (34).

Treatment options are limited to frontline ACTs because of a high prevalence of resistance to older antimalarials such as sulfadoxine-pyrimethamine (SP), chloroquine (CQ), and amodiaquine (AQ) (32). Current National Malaria Control Program (NMCP) recommends either AL or artesunate plus AQ (ASAQ) as first-line for the treatment of malaria in Burkina Faso. Due to prevalent infections, especially in rural, underdeveloped areas, the NMCP policy is to only treat symptomatic cases of malaria to limit drug resistance to the first-line ACTs. Outside of anti-malarial treatment, most malaria control is achieved through vector control. LLINs are the primary tools employed for limiting vector contact with humans and reducing the vector population through the impregnated insecticides in the nets (pyrethroid insecticides). To a lesser extent, IRS operations using pyrethroid and carbamate insecticide classes are performed in some areas. Unfortunately, mosquito resistance to both of these insecticides is widespread, partially due to their widespread application in agricultural operations that are prevalent in the same afflicted villages, especially cotton and rice production (35). New tools will be critical to achieving malaria control in the country.

Anti-vector strategies are critical to the efficacy and sustainability of any malaria control measure, because the efficiency of vector transmission is so strong. Further, they are key for sustaining the efficacy of antimalarials. However, LLINs seems to have reached their maximum efficacy for reducing malaria further, and new chemistries for LLINs are slow to be implemented. Further, insecticide resistance among vectors is now widespread (36). Thus, new anti-vector tools are necessary to add combinatorial chemistries and new target sites to combat vector transmission.

Our study is designed to study a new vector control tool, repeated high-dose IVM MDA (the intervention), through its integration into the regular, 4-monthly/season SMC delivery platform and with other existing malaria control methods conducted in the study villages. The intervention, generic IVM or IVM placebo (e.g. Iver P®, Elea Labs; 6 mg tablet) in 300 µg/kg dose estimated by height bands, will be administered orally for 3 days to eligible individuals NOT receiving SMC. Per the package insert, dosing of IVM or placebo will be according to height to estimate weight: 90-119 cm (15-25 kg) = 1 tablet/day for 3 days; 120-140 cm (26-44 kg) = 2 tablets/day for 3 days; 141-158 cm (45-64 kg) = 3 tablets/day for 3 days; >158 cm (65-84 kg) = 4 tablet/day for 3 days. Rounds will be administered in a monthly schedule from July-October (4X) as a 3-day course to all eligible persons per exclusion/inclusion criteria. The intervention period will last two rainy seasons (2019-2020). The interventional drugs will be

administered by the study personnel working with CHWs via the door-to-door delivery (DDD) method and using directly and then non-directly observed therapy (DOT/NDOT), whereby the first day of treatment of each month will be given by the study team and treatments for the second and third days will be given by the caregiver at home for each monthly round. These delivery methods were chosen based on clinical trial data suggesting they are the optimal balance of being logistically simple while achieving optimal coverage (37).

The hypothesis is that MDA with ivermectin coinciding with SMC rounds and on top of other standard malaria control interventions currently conducted (four SMC rounds to 3-59 month old children, high LLIN coverage, and IPTp) will significantly reduce the incidence of malaria in children compared to MDA with placebo.

2.3. Potential Risks and Benefits

2.3.1. Potential Risks

The primary potential risks from participating in the intervention include adverse reactions to the study drug, ivermectin. IVM is well-tolerated, but can induce Mazzotti-type reactions in helminth-infected patients that are linked to parasite lysis and clearance in heavily-parasitized patients after their first treatment in MDA (38). The most common of these adverse reactions are abdominal pain, urticaria/rashes/pruritis, fever and chills, gland or eye reactions, loss of appetite, constipation, diarrhea, nausea, fatigue, vomiting, dizziness, (Appendix A & B) (29, 39). However, many of the villages in the southwest region of Burkina Faso participate in yearly anthelmintic MDAs with IVM and albendozole that have occurred for more than a decade, and so worm burden is absent or low in many villagers. In RIMDAMAL I, evidence of *Wuchereria bancrofti* infections in our study villages by xenomonitoring was absent, and a cross-sectional examinations of children 5-10 years for STHs revealed only 2 cases of ascariasis. Out of 2712 participants, we recorded only 8 adverse events of mild or moderate intensity that were determined to be possibly or probably related to taking IVM in a MDA. Per the Mectizan label (Appendix A), severe skin reactions have been very rarely reported following IVM MDA, but the only confirmed IVM-related serious adverse events (SAE) have been in individuals heavily-infected with *Loa loa* due to lysis of parasites. However *Loa loa* is not present in Burkina Faso, and the participants in the study villages will be excluded from participating in IVM MDAs if they have traveled to countries where *Loa loa* is endemic.

A recent review of neurological SAE from ivermectin treatment outside an onchocerciasis indication was published by Chandler from an analysis of data in VigiBase (40). Most of these SAE (20/28) were cases where concomitant medications were given with ivermectin. No participant in RIMDAMAL I had a SAE

that was determined to be related to IVM treatment, and none had the SAE reported in Chandler's review.

Caution and a physician's consult are indicated before IVM is used by pregnant and breast-feeding women. Importantly, as in RIMDAMAL I, this study will avoid treating pregnant women by screening those of reproductive age with a urine pregnancy rapid test before each MDA, and we will only treat those women breast-feeding infants >1 week old, as per the label.

Another recent review analyzed the safety of ivermectin treatment in children <5 yrs. of age and weighing less than 15 kg, most for a scabies indication (41). The authors stated that while more studies are required to establish the safety profile of ivermectin in this age group, they note that the drug was well-tolerated and without any evidence of serious or long-term adverse events in the available literature.

Our currently proposed 3x300 μg/kg dosing regimen (estimated by height bands) has been studied in the IVERMAL trial, whereby it was administered once alongside DP in a small cohort of Kenyan adults (age 18-50 years) with uncomplicated malaria (28). The regimen was tested as way to maximize the time of mosquitocidal activity in treated persons' blood, and because high doses have been remarkably well-tolerated in the literature (23-26, 42, 43). Overall, the regimen was well-tolerated in their patients, with 8 AE in 48 ivermectin-treated patients and 9 AE in 46 placebo-treated patients, with no statistically-significant risk differences of AE between the groups. Treatment-related AE were confined to minor visual disturbances and occurred in 4% (2/48) of treated participants, while no SAE were observed.

Our study will administer the 3x300 μg/kg (estimated by height bands) regimen in 4-monthly rounds over 2 seasons and to approximately 1800 persons who are ≥90 cm height (and ≥ 5 years of age) in each study village. Thus, the greatest potential risk of this trial is in giving this dosing regimen more frequently (monthly x 4 months each season), to more participants, and to a broader range of age groups than in the IVERMAL trial. Because the length of mosquitocidal activity from this dosing regimen is a key determinant in the large expected effect size on malaria incidence (44), and also this 4-monthly schedule achieves logistic synergy with standard-of-care SMC treatment of children < 59 months old in the same households, an alternative to the 4-monthly treatment schedule may not be feasible relative to the project's goals. It may be possible to give a 1x400 μg/kg dose (estimated by height) schedule each month instead of the 3x300 μg/kg dose (estimated by height) schedule, if the latter is deemed as not well-tolerated after the first MDA. However, this change could affect our blinding, and preliminary modeling data we have obtained suggests a nearly a week less mosquitocidal activity would be achieved in the treated population, which would lessen the expected effect size considerably and so this may also not be feasible.

Other risks are minimal, and include psychological harm to study participants if their private information are disclosed, but we will make every effort to prevent this. Small bruising at the site of the finger stick and/or at the site of venipuncture are also possible, as is syncope from blood draws, but these procedures will all be conducted by the study clinical team who will be trained to treat these possible problems.

In summary, the risks to the subjects are moderate with respect to receiving the intervention (IVM MDA at the aforementioned dose and frequency) and minimal with respect to the clinical team taking blood samples or the investigators making public their personal information accidentally. These risks are reasonable in relation to the anticipated benefit of significantly less malaria among the populace, which causes yearly debilitating disease and death in the communities in which we will work.

2.3.2. Known Potential Benefits

Ivermectin is a potent endectocide that is approved around the world for the treatment of patients infected with many different parasitic worms (*Onchocera volvulis*, *Wuchereria bancrofti*, *Strongyloides stercoralis*, as well as patients infected with scabies mites (*Sarcoptes scabei*). It also has documented activity against many other internal and external parasites, including some STHs such as roundworms (*Ascaris lumbricoides*) and whipworms (*Trichuris trichuria*), and head lice (*Pediculus humanus capitis*) (45). Thus, control of NTDs caused by these parasites in treated participants is a known potential benefit. Also, the known potential benefits of the research to the participants is the expected reduction in malaria incidence among participants who live in the intervention villages, especially among those vulnerable groups most at risk of uncomplicated and complicated malaria episodes, children and pregnant women. In RIMDAMAL I, the children of the control arm experienced a mean incidence of 2.49 malaria episodes as compared to 1.99 malaria cases in the intervention arm over the 18 week trial during the rainy season. This was an approximate 20% reduction in malaria incidence among the treated cohort (or a risk difference of approximately 0.5 episodes/child). In this study, we have modeled a reduction of malaria incidence in the child cohort of approximately 43%.

Furthermore, despite not receiving the intervention, those living in the control arm villages will also receive potential benefits of increased and frequent health care afforded by the regular active case detection visits from the study nurses and other members of study clinical team, which includes screening for malaria-related febrile illness and other general health problems, and subsequent free consultation and treatment with antimalarials and other medicines. The value of these benefits were reported to us by the populace in the control villages of the RIMDAMAL I trial. These potential health benefits might be expected to translate to psychological benefits from feeling supported in their

physical care, and economic benefits from a healthier workforce being better able to complete their jobs and sell their goods.

3. OBJECTIVES AND OUTCOME MEASURES

3.1. Study Objectives

3.1.1. Primary

- The primary study objective is to assess the impact of a combined approach of repeated IVM MDA and SMC on malaria incidence in children, with the purpose of testing the superiority of IVM compared to placebo for reducing malaria incidence. Our hypothesis that IVM MDAs (the intervention), coinciding with standard of care antimalarial procedures in Burkina Faso (four SMC rounds during the rainy season, maximum LLIN coverage and IPTp for pregnant women), will significantly reduce the incidence of childhood malaria in the intervention arm compared to the control arm. The IVM MDAs will consist of generic IVM or IVM placebo (e.g. Iver P®, Elea Labs; 6 mg tablet) given monthly from July-October (4X) as a 3-day course to all eligible persons who meet inclusion criteria (≥90 cm and not treated with SMC (≥ 5 years), not pregnant or breast feeding an infant less than 1 week old). Dosing of IVM or placebo will be according to height as indicated on the package: 90-119 cm = 1 tablet/day for 3 days; 120-140 cm = 2 tablets/day for 3 days; 141-158 cm = 3 tablets/day for 3 days; >158 cm = 4 tablet/day for 3 days.

3.1.2. Secondary

The study's secondary objectives are several-fold. This first secondary objective is safety:

- To measure whether the IVM MDAs will increase harms in the participants.

We also aim to characterize entomological, parasitological and pharmacological indices associated with the primary outcome. Because IVM MDA primarily effects the survivorship of malaria vectors that blood feed on treated people, there are several related effects we expect will be able to mechanistically explain the reduction in clinical incidence among children that we should observe in the intervention arm.

- To measure the entomological indices (mosquito survival rate after blood feeding, mosquito population age structure, sporozoite rate if they are infected with *Plasmodium* parasites, human exposure to *Anopheles* mosquito bites) between the intervention and control arm and over the time of the intervention phase.
- To measure the parasitological indices obtained from blood samples collected during the active case surveillance of cohort children, between the intervention and control arms and over the

time of the intervention phase. These indices are asexual parasite prevalence, species, density, the multiplicity of infection, and the molecular force of infection (mFOI).

- To link the pharmacokinetics-dynamics of ivermectin in a sub-cohort of the treated study population to mosquito blood feeding and survival.

3.2. Study Outcome Measures

3.2.1. Primary

- The incidence of malaria episodes in cohort children ≤10 years of age as assessed by active case surveillance. Malaria incidence in children is the most clinically-relevant outcome measure in this field setting from an anti-vector intervention that targets blood feeding mosquitoes, and its reduction following repeated IVM has been validated from our prior RIMDAMAL I study. Study nurses will visit each child weekly to monitor for malaria episodes. At each visit, a temperature reading will be recorded. If the temperature is ≥37·5°C and/or history of fever in the last 24 hours, a blood sample will be taken and assessed by rapid diagnostic test (RDT) for *Plasmodium* spp. If this is also positive, this will be considered a positive malaria episode.

3.2.2. Secondary

- AE monitoring will occur both actively and passively. All AE will be graded and analyzed by seriousness, intensity and causality. AE monitoring in this study is crucial to properly weigh the potential benefits vs. potential risks of the study.
    - In the entire enrolled populace, passive monitoring of AEs will occur through spontaneous reporting of events to the study clinical team, and recorded on CRFs. AEs will be recorded from the entire enrolled populace, regardless if they were treated with ivermectin/placebo or not eligible to take the intervention. AEs will also be actively monitored on the days of distribution of ivermectin/placebo through direct questioning of AEs and recording on CRFs by study nurses for all participants. AE will be recorded over the intervention period occurring during the 1st and 2nd rainy seasons. More specifically, AEs will be recorded from the start of the first MDA of each rainy season to 1 month after the last MDA of that season.
    - For those children enrolled in the active case detection cohort, where children are visited weekly to assess for malaria incidence, active monitoring of AEs will occur through direct questioning of AEs by the study team. Additionally, passive monitoring of AEs will occur by

participants spontaneously reporting directly to the nurses when the nurses are in the villages performing active case detection of malaria in the child cohort, or spontaneously reporting indirectly to the nurses via communication through the village community health worker (who will then communicate the AE directly to the nurse or field physician).

- For women that become pregnant during the intervention period, monitoring for birth outcomes will be conducted. Pregnancies will be followed in both arms of the study.

- Entomological indices will provide a first-order mechanistic explanation of the intervention's effect on malaria incidence (the primary outcome): Wild, blood-fed, indoor-aspirated, *Anopheles* will be held in cages and scored for survival rates over time, which will be analyzed across arms. The age structure of captured *Anopheles* will be analyzed over time and analyzed across arms. Captured wild mosquitoes will be dissected and analyzed for sporozoite infection rates over time and analyzed across arms. A cohort of participants' sera immuno-reactivity to an *Anopheles* saliva antigen will be analyzed over the intervention period of each season.

- Parasitological indices will provide a second-order mechanistic explanation of the intervention's effect on malaria incidence (the primary outcome): Prevalence, species and densities of asexual parasitemias will be scored from stain blood smears and analyzed over time and across arms, in both blood samples taken during the active case surveillance of cohort children, and in cross-sectional sampling of the whole study population. The genetic markers of parasites in participant dried blood spots will be analyzed for the multiplicity of infection, and the molecular force of infection over time. Samples will also be obtained at additional timepoints in a subset of participants, in order to obtain a baseline estimate for prevalence estimates. These finger prick blood samples will be collected during the dry seasons in 2020 and 2021, during the wet season in 2021 and at up to 4 other timepoints throughout the year. Baseline samples will allow for better assessment of changes occurring with IVM and SMC drug pressure. (This additional sampling will utilize a separate information sheet and consent document. Only participants who consent to participate in the additional sampling will do so.)

- Pharmacokinetics-dynamics will be studied in a sub-cohort of participants to link the presence of drug with mosquito biting and survival: Ivermectin in blood samples from different treated subjects (different age strata and genders) will be quantified and used to construct models to estimate and compare the pharmacokinetic parameters (e.g. C_{max}, $T_{1/2}$) across strata in blood. Entomology sampling in the houses of these participants following treatment will collect blood fed mosquitoes that will be 1) analyzed for survival, 2) tested for ivermectin in their blood meals, and 3) for the genetic signatures of the studied participants in the blood meal.

4. STUDY DESIGN

A cluster randomized trial will be conducted in a single region of southwestern Burkina Faso over two consecutive rainy seasons and designed integrate repeated high-dose IVM MDA into the existing monthly SMC delivery platform and distribution of LLINs performed by CHWs. The hypothesis is that IVM MDAs coinciding with SMC rounds will significantly reduce the incidence of childhood malaria compared to the standard of care anti-malaria interventions (SMC, LLIN distribution, IPTp) alone. Twelve villages (clusters) in the region will be recruited to participate in this phase 3, double-blind, parallel-assignment trial with two arms randomized in a 1:1 ratio. A cluster-randomized trial is necessary because the intervention is IVM MDA which primarily targets the mosquito population that randomly feed on the people in the village, thus the effect is village-wide. Village population size is expected average approximately 360 people, and all eligible persons in each village will be asked to enroll, thus giving us an enrolled population of approximately 5000 participants. These will be otherwise healthy individuals who live in a hyper-endemic malaria region. Thus, most are infected with malaria parasites during the rainy season when vector numbers and parasite transmission peaks, and children suffer a high burden of malaria due to the inadequate immunity they have developed against *Plasmodium* infections. Our primary outcome is the incidence of malaria episodes in children ≤ 10 years of age over two rainy seasons. Safety of IVM will be assessed as a secondary outcome to ensure the intervention does not increase harm to the populace, and entomological, parasitological, and pharmacokinetic parameters also assessed as secondary outcomes to provide a clear understanding of the basis of IVMs impact in the context of this trial.

The sample size is based on a mathematical modeling of the intervention on the primary outcome and suggests we should observe an effect size in the intervention arm over the control arm of 43.1%, assuming a rate incidence in our 0-10 yr. old cohort of 1.088 malaria episodes/child/year and 0.619 malaria episodes/child/year in the control and intervention arms, respectively. Using an intra-cluster coefficient of 0.258 and setting the α=0.05, 6 clusters/arm with a minimum of 48 children/cluster in our child cohort is necessary to detect a significant difference in the rates between the arms with 80% power. In January 2019, the sample size modeling exercise was re-performed because it was learned that that villages in the Diebougou health district (the study site) were expected to receive new Interceptor G2 LLINs prior to the 2019 rainy season. These new LLINs are made with two different insecticides (chlorphenapyr and alpha-cypermethrin) to circumvent the prevalent pyrethroid-resistance seen in Burkina Faso the much of SSA. Thus, we assumed a 12%-50% reduction in malaria incidence in both arms due to distribution of these nets. Keeping with an effect size of 43.1% in the intervention am over the control arm, using an intra-cluster coefficient of 0.2, and increasing the sample size to 100 children/cluster in our child cohort, we need between 4.9 and 5.5 clusters/arm to detect a significant

difference in the rates between the arms with 80% power. The primary outcome will be analyzed as intention-to-treat, meaning it will include all enrolled cohort children (≤10 years old) in the groups to which they were randomly assigned, regardless of their compliance with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol. Importantly, all eligible cohort children ages 3-59 months are expected to receive SMC, and all eligible cohort children ≥90 but not taking SMC are expected to receive either ivermectin or placebo as the intervention. However all these children, no matter their treatment, will be included in the primary outcome analysis. The incidence of episodes from the children cohort will be used as the primary measurable outcome to evaluate the impact of the intervention when compared to the control arm. The primary analysis will use either cluster-level analyses, or multilevel/hierarchical regression modeling techniques to account for clustering at the level of the randomization unit (village), as well as analyze individuals with multiple time points where both unadjusted and adjusted analyses will be performed. The unadjusted as well as adjusted estimates depicting the impact of the intervention versus control will be reported along with 95% confidence intervals. The time-to-first infection will also be analyzed using a survival analysis within each arm and calculation of a hazard ratio with 95% confidence interval. Secondary data generated from Aim 1 will include adverse events (AE) and serious adverse events (SAE). The risk of SAE and AE will be compared between intervention and control arms by calculating risks ratios and attributable risks with 95% confidence intervals. Standard statistical hypothesis testing, as well as estimating the effect sizes and confidence intervals, will be used to measure the differences in entomological, parasitological, and pharmacokinetic secondary outcomes between arms and the exploratory outcome measures.

The pre-intervention phase will take up to 1 year and consist of writing and finalizing all protocols and SOPs, securing all regulatory documents, permissions and approvals, hiring and training study staff, setting up and the field station, securing study equipment, supplies and drugs, engagement, randomization and allotment of study villages, and enrolling and consenting all study participants.

At the start of the intervention phase, expected to be July of the 1st rainy season, the first of four SMC rounds will occur, and continue at the beginning of each month from July-October. On the same dates, and leveraging the SMC infrastructure, our IVM MDA rounds (or placebo) will occur in each village. Pregnant women will be encouraged to receive their publicly-provided antenatal care treatment, including at least three SP treatments once/month after the start of their second trimester (per WHO and Burkina Faso Ministry of Health (MoH) policy). The trial staff will work with regional and local health authorities, including community health workers assigned to each village, to administer the intervention. The two arms will specifically receive:

1) Standard of care:

a. Active LLIN distribution in the villages will be maintained by the MoH. Time of distribution of new G2 bednets will be recorded.

b. SMC given monthly from July-October (4X) with SP+AQ (500/25 mg S/P and 153 mg AQ for children 12-59 months; 250/12.5 mg S/P and 76.5 mg AQ for children 3-11 months. SMC will be provided by the Burkina Faso MoH.

c. IPTp provided to all pregnant women with SP. WHO and Burkina Faso MoH policy recommends at least 3 treatments, 1 month apart, starting in second trimester. Provided by the Burkina Faso MoH ((500/25 mg S/P per tablet, 3 tablet dosage (1500/75 mg S/P)).

2) Study intervention:

a. IVM or placebo (6 mg tablet) given monthly from July-October (4X) as a 3-day course to all eligible persons per exclusion/inclusion criteria (≥90 cm and not treated with SMC (≥ 5 years), not pregnant or breast feeding an infant less than 1 week old). Per package insert, dosing of IVM or placebo will be according to height: 90-119 cm = 1 tablet/day for 3 days; 120-140 cm = 2 tablets/day for 3 days; 141-158 cm = 3 tablets/day for 3 days; >158 cm = 4 tablet/day for 3 days.

A study nurse will be assigned to each village to work with the village CHWs to distribute the study drugs and LLINs. LLINs and SMC/IPTp drugs will be health services provided by the Burkina Faso MoH NMCP. Generic IVM and placebo will be purchased through the study from Laboratorio Elea or another provider. Malaria episodes in enrolled study village children ≤10 years of old will be determined by active case surveillance via study nurses visiting each child weekly with the CHW during the intervention to monitor for malaria episodes. An uncomplicated malaria episode will be defined as axillary temperature ≥37.5 °C (with adjustment for temperature taken at other locations) and/or history of fever in the last 24 hours, *and* a positive RDT for *Plasmodium* spp. Complicated malaria is defined in Appendix D. As per MoH guidelines, a standard course of AL will be administered to all children with uncomplicated malaria cases, while complicated malaria cases will be referred to the nearest district hospital to for treatment with either intravenous quinine or artesunate. Blood will also be preserved on slides and filter papers for later analysis. The nurse will record positive malaria episodes in children, as well as any spontaneously-reported AEs communicated by the study populace, into CRFs and treat them as able or refer them to the district hospital. Throughout the intervention phase, entomology teams will capture mosquitoes from intervention and control clusters, and parasitology teams will sample blood from selected study villagers along transects and at cross-section.

The intervention phase will be completed one month following the 8th SMC/IVM MDA round at the end of the 2nd rainy season, and the clinical component of the trial will be closed. Limited cross-sectional mosquito and blood sampling will occur in study villages in the 3rd rainy season, after the intervention is complete, to analyze any potential changes in mosquito or parasite populations in the villages. The blood sampling schedule is in table 4.

Samples will also be obtained at additional timepoints from all cross-sectional households and select others. A separate information sheet and consent document will be used for this purpose and participants will be approached separately about participating in this additional sampling. These finger prick blood samples will be collected during the dry seasons in 2020 and 2021, estimated to be between March and June following MDA , during the wet season in 2021 and at up to 4 other timepoints throughout the year. Blood samples will be drawn via finger prick and will be preserved on slides and filter papers for later analysis.

Table 3: Summary of the study groups and schedule for blood sampling.

Group	Number to sample	Ages	What and when samples collected BS=blood smear FP=filter paper				
Child cohort (followed with active case surveillance)	~1800	≤10 yr. olds	BS&FP -when malaria diagnosed	BS&FP -before season	BS&FP -between the second and third MDA each season	BS&FP -post season	BS&FP -dry season/ post intervention (only from select participants)
Households# on village transects (3 villages/arm; ~8 households/village)	~380	all note: ≤10 yr. olds will be sampled in the ACD cohort		BS&FP -before season	BS&FP -between the second and third MDA each season	BS&FP -post season	BS&FP -dry season/ post intervention
PK-PD modeling cohort	180	5-10yo (n=30 per arm) 11-18yo (n=30 per arm) ≥19yo (n=30 per arm)	Each participant sampled for capillary blood up to 5 of the following time points after their last dose of IVM: 0h (pre-last dose), 1h, 4h*, 8h, 12h*, 24h, 48h, 52h, 60h, 72h, 7d*, 14d, 21d and 28d. **venous blood will be collected simultaneously at these time points*				
# Hemoglobin analyses will also be performed on the capillary blood from a sub-sample of adults and children over the study using a Hemocue (or other) device.							

Trial monitoring will be according to the Data Safety and Monitoring Plan and an independent Data Safety and Monitoring Board (DSMB) will established by the DMID to provide safety review and trial guidance, including advice on continuing, modifying or terminating the study. The study monitor will be an in-country contract research organization (CliMAfrica-CRO or other) who will provide external monitoring for the study. During the intervention phase, trained clinical trial monitoring experts from the CRO will conduct at least six monitoring visits (before, during and immediately after the intervention phase of the study, in rainy seasons 1 and 2). These will include assessment of site compliance and standard operating procedures, review of consents, assents, training documents, research/study approvals and data collection forms, review of site facilities, and laboratory sample storage, shipment, and labeling. An interim analysis of the safety data will be conducted after the 2rd MDA occurs in the first rainy season, and also in-between the first and second rainy seasons.

5. STUDY ENROLLMENT AND WITHDRAWAL

Malaria-endemic villages in southwestern Burkina Faso that will participate in SMC in season 1 of the study will be recruited to participate. The subject population in this region consists of West Africans mainly from the Mossi, Bobo, Dagara, Lobi and Fulani ethnic groups and who are mostly subsistence farmers and traders. All eligible village residents will be asked to enroll, which encompasses people of all ages and genders and reproductive capability, and small to medium size villages ranging between 200-500 people will be recruited; per our power analysis, we require 7 villages per arm and ~100 children who are ≤10 years of age per cluster. If possible, we will also attempt to choose villages that have distinct boundaries and non-populated buffer zones of agricultural fields or bush land surrounding them in order to minimize mosquito movement between control and intervention clusters and between study and non-study villages.

5.1. Subject Inclusion Criteria

Subjects must meet all the inclusion criteria in order to be eligible to participate in the study. Subject Inclusion and Exclusion Criteria will be confirmed by a study clinician licensed to make medical diagnoses. No exemptions will be granted on Subject Inclusion/Exclusion Criteria in this DMID-sponsored study.

We will attempt to enroll all inhabitants of selected villages who the leaders and majority of village heads-of-household first give their verbal consent to participate in the study.

Inclusion criteria are:

- Residence in selected study village
- Able to understand the information and willing to give consent or assent (age 12-18) and parent/guardian consent if study participant age is < 18 years of age.

We will attempt to enroll all children who live in the selected and verbally-consented villages in our active case surveillance cohort.

Active case surveillance cohort inclusion criteria:

- Residence in selected study village

- ≤10 years of age
- Parent/guardian consent

5.2. Subject Exclusion Criteria

Exclusion criteria for participating in the intervention (IVM/placebo MDA):

- Residence outside of the study village
- Height < 90 cm (*note: if subject becomes ≥90cm over course the trial, this exclusion criteria will no longer be valid in subsequent MDA)
- Current treatment with SP+AQ as part of SMC (restricted to children 3-59 months old) (*note: if subject discontinuous SP+AQ treatment because they become older than 59 months over course the trial, this exclusion criteria will no longer be valid in subsequent MDA)
- Permanent disability or serious medical illness that prevents or impedes study participation and/or comprehension
- Pregnancy (screened for in women of child-bearing age [ages 12-45] using a pregnancy urine rapid test [e.g. SD Bioline hCG] the week prior to each MDA), as well as older females who have not yet had menopause
- Breast feeding if infant is within 1 week of birth
- Known allergy to ivermectin
- Possibility of *Loa loa* infection as assessed by travel history to Angola, Cameroon, Chad, Central African Republic, Congo, Democratic Republic of Congo, Equatorial Guinea, Ethiopia, Gabon, Nigeria, and Sudan.
- Enrolled in any other active clinical trials

Active case surveillance cohort exclusion criteria:

- Residence outside of the study site
- Permanent disability, serious medical illness that prevents or impedes study participation

Additional PK/PD cohort exclusion criteria:

- Concurrent use of drugs known to interfere with CYP3A4 metabolism within the past 14 days. (Section 6.6)
- Hemoglobin < 7g/dL

5.3. Treatment Assignment Procedures

5.3.1. Randomization Procedures

This will be a cluster (village)-randomized trial. Once the chiefs/leaders and heads-of-households of all fourteen selected villages give their verbal consent to participate following informational and question and answer meetings with the study team, a village representative and the CHWs representing each village will be asked to participate in a public randomization event at the facilities of the district health authority, attended by the district medical director and members of the study team. In front of the attendees, the numbers "1" and "2" will be written on 7 cards each, which will be sealed in identical opaque envelopes, mixed in a container, and then randomly pulled from the container by each village representative. Villages will be assigned to the arm written on the card selected by this representative, and the procedures will be video recorded. These arm designations will be linked to the masked active ingredient tablet or placebo (below).

5.3.2. Masking Procedures

The study pharmacist in charge of the drug stock rooms will originate the masking, written on three paper copies and put in identical and sealed opaque envelopes, which will be kept: 1- In the inventory paperwork binder at the drug stock room, and with each PI (2-with Dr. Foy in the Investigator's Brochure, 3- with Dr. Parikh). The study pharmacist will allocate the IVM and placebo tablets for each IVM MDA round according to the original randomization throughout the trial, and distribute the drug in sealed containers labeled by a code (e.g. "Village $X_{(1-7)}$ – Arm 1" and "Village $Y_{(1-7)}$ – Arm 2") to the clinical team prior to each round.

5.3.3. Reasons for Withdrawal and Discontinuation of Study Product Administration

Participants (or parent/guardians) may voluntarily withdraw their consent/assent at any stage for study participation without penalty or loss of benefits to which they are otherwise entitled.

An investigator may withdraw a subject from receiving the study product for any reason. Follow-up safety evaluations will be conducted, if the subject agrees. If a subject withdraws or is withdrawn prior to completion of the study, the reason for this decision must be recorded in the case report forms (CRFs).

The reasons, might include, but are not limited to the following:

- Screening error resulting in incorrect enrollment (discovery that the subject did not meet the required inclusion/exclusion criteria)
- Withdrawal of assent/consent at any stage or the subject is not willing to continue in the study (or withdrawal of consent by the parent/guardian to keep his or her child enrolled).
- Suspected or confirmed allergic reaction to the study drugs.
- Safety reasons as judged by the investigators or the DSMB after a meeting to review safety.
- Subject no longer meets eligibility criteria (e.g. becomes pregnant)
- Subject becomes noncompliant
- Medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator might compromise the safety of the subject, interfere with the subject's successful completion of this study, or interfere with the evaluation of responses
- Subject lost to follow-up
- Determined by a physician’s discretion to require additional therapy not indicated in the protocol to ensure subject’s health and well-being (or treatment failure, if applicable)

The investigator should be explicit regarding study follow-up (e.g. safety follow-up) that might be carried out despite the fact the subject will not receive further study product. If the subject consents, every attempt will be made to follow all AEs through resolution. The procedures that collect safety data for the purposes of research must be inclusive in the original informed consent or the investigator may seek subsequent informed consent using an IRB/IEC-approved consent form with the revised procedures.

The investigator will inform the subject that already collected data will be retained and analyzed even if the subject withdraws from this study.

5.3.4. Handling of Withdrawals and Discontinuation of Administration

Participants who discontinue in the study or withdrawal their assent/consent will always be asked about their reason(s) for discontinuing and about any adverse events they may have experienced. If a person discontinues, it should be determined whether:

1. They discontinue treatment, but continue their consent for the data capture and continue follow-up. These subjects will be considered 'off drug study/on study" and follow the same schedule of events except for participation in the interventions.
2. They discontinue all future activities in the study, but continue their consent for the data captured up to that point to be used in the research.
3. They discontinue all future activities in the study and withdrawal their consent for any past data captured to be used in the research.

These scenarios will be recorded in Case Record Forms (CRFs).

5.3.5. Subject Replacement

Subjects that have discontinued the study prematurely will not be replaced. New inhabitants that move into the study area will be approached for consent during the study.

5.3.6. Termination of Study

The study's safety data will be analyzed by the DSMB after the interim analyses conducted soon after the 2rd MDA, and another conducted after the first full season of treatment. A detailed plan for interim analysis, any planned statistical adjustments to be employed as a result of interim analysis, the provisional stopping rules and how the stopping rules will be applied, will be drawn up prior to the start of the interim analysis.

Following the recommendation from the DSMB, the sponsor reserves the right to temporarily suspend 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 investigators. 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 DMID/NIH, the CSU and Yale IRBs and the Comité d'Ethique of the IRSS, and provide the reason for the

suspension or termination. The study may also be suspended or terminated at the discretion of the DMID/NIH based on funding decisions.

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the study subjects and assure appropriate therapy or follow-up for the subjects, as necessary. The investigator will provide a detailed written explanation of the termination to the IRBs and IEC.

6. STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1. Study Product Description

6.1.1. Acquisition

Product 1 – generic IVM

IVM (generic IVM, 6 mg tablets) will be purchased either from Laboratorio Elea, Argentina, who also produced these for the IVERMAL trial (48), or from another supplier. These will be shipped from the production facility to Burkina Faso with a tracking number on a commercial transport service, and transported to the study site with all the required regulatory documents. Electronic temperature monitors will be included during shipping and transport to ensure the quality of the product is not compromised during shipment.

Product 2 - placebo

Placebo (e.g. sucrose) will be purchased from either from Laboratorio Elea, Argentina, who also produced these for the IVERMAL trial (48), or from another supplier. These will be shipped from the production facility to Burkina Faso with a tracking number on a commercial transport service, and transported to the study site with all the required regulatory documents. Electronic temperature monitors will be included during shipping and transport to ensure the quality of the product is not compromised during shipment.

6.1.2. Formulation, Packaging, and Labeling

Product 1 –generic IVM

See the package insert.

Product 2 - placebo

To be determined by the manufacturer.

6.1.3. Product Storage and Stability

Product 1 – generic IVM

Per the package insert, the product will be maintained in a climate-controlled study drug storage room that is <30°C and free from high humidity. When traveling to the villages, the product will be kept in cool boxes during transport.

Product 2 - placebo

Similar to the package insert, the product will be maintained in a climate-controlled study drug storage room that is <30°C and free from high humidity. When traveling to the villages, the product will be kept in cool boxes during transport.

6.2. Dosage, Preparation and Administration of Study Intervention/Investigational Product

IVM or IVM placebo will be given monthly from July-October (4X) over 2 consecutive seasons as a 3-day course to all eligible persons per exclusion/inclusion criteria. Similar to the Mectizan and Iver P package inserts, dosing of IVM or placebo will be according to height as an estimate for weight (Table 5)

Table 4: Dosing of ivermectin or placebo

Height (cm)	Estimated weight (kg)	# of Tablets	Total mg per dose	Total mg per 3-day course
90-119	15-25	1 tablet	6mg	18mg
120-140	26-44	2 tablets	12mg	36mg
141-158	45-64	3 tablets	18mg	54mg
>158	65-84	4 tablets	24mg	72mg

The study pharmacist (who will be unblinded) will allocate the IVM and placebo tablets for each IVM MDA round according to the original randomization throughout the trial, and distribute the drug in sealed containers labeled by the codes "Village $X_{(1-7)}$ – Arm 1" and "Village $Y_{(1-7)}$ – Arm 2" to the clinical team no more than 2 days prior to each round.

6.3. Modification of Study Intervention/Investigational Product for a Subject

If the 3x300 µg/kg dose (estimated by height) schedule is observed to incur drug-related AE (see section 2.3.1 and Appendix B for known drug-related AE) in more than 10% of the treated population after the first MDA by the study physician, the dosing schedule may be modified to a 1x400 µg/kg dose (estimated by height) schedule each month for the remainder of the trial. This would only change the number of consecutive days a dose of ivermectin (or placebo) would be given per MDA, from 3 consecutive days per MDA to only once per MDA (see Table 5); it would not change the number of tablets or the total mg per dose corresponding to each height band. This change in dosing will be done in an online or phone ad hoc consult with the DSMB in the month after the 2nd MDA, and may depend on the follow-up clinical evaluations of participants. The clinical reasons for this change will be written into a report authored by study physician prior to the next MDA and will be sent to the IRBs/EC, CRO and to the DMID prior to the next MDA.

If an individual participant is determined unable to take a dose of IVM/placebo due to a known allergy to the drug or other reason, the product or dosage will not be modified in any way. Instead, this and/or all future doses will not be administered to the participant and this will be noted accordingly on the participant's case report form.

6.4. Accountability Procedures for the Study Intervention/Investigational Product(s)

The study drugs will be shipped from the supplier directly to the IRSS in Burkina with all appropriate permits and documentations. They will be transported to the drug stock room at the field site, accounted for by the unblinded study pharmacist, dispensed as describe in 6.2 above in containers labeled per village and in accordance with the blind, and distributed to the clinical team no more than 2 days prior to their administration by the clinical team.

The Investigator is responsible for ensuring that a current record of product disposition is maintained and product is dispensed only at the study site by authorized personnel. Records of product disposition, will consist of the date received, date administered, quantity administered, and the subject number to whom the drug was administered.

The unblinded study pharmacist will be responsible for maintaining accurate records of the shipment and dispensing of the investigational product. The pharmacy records must be available for inspection by the CRO at any time.

Unused investigational product will be stored in the designated climate-controlled study drug storage room <30°C and free from high humidity in the Investigational Pharmacy until clinical trial accountability is completed. At study termination, all unused investigational product will be disposed of in accordance with the manufacturer's operation protocol following complete drug accountability and monitoring.

6.5. Assessment of Subject Compliance with Study Intervention/Investigational Product/Investigational Device

The clinical team will distribute the drugs door-to-door at the same time as the CHWs distribute the SMC door-to-door to the village children, at the beginning of each treatment round month (July, August, September, October) in two consecutive seasons. Treatment with the study drugs will be via DOT/NDOT, and unused drug will be returned to the pharmacist after each MDA. Administration will be documented on the CRFs in the nurse tablets.

6.6. Concomitant Medications/Treatments

No medications are restricted on the Iver P and Mectizan package inserts, so none will restrict treatment eligibility. All concomitant medications known to be taken during the study by study participants will be recorded in the appropriate sections of the CRF with indication, dose information, and dates of administration.

However, due to potential CYP3A4-mediated drug-drug interactions, participants in the PK/PD sub-study will not be eligible if they have received any of the following medications within 14 days of IVM administration:

- Carbamazepine
- Clarithromycin
- Erythromycin (oral)
- Ketoconazole
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampin
- Halofantrine
- Any other medication known to significantly affect CYP450 metabolism.

7. STUDY SCHEDULE

7.1. Recruitment

Malaria-endemic villages in southwestern Burkina Faso that will participate in SMC in season 1 of the study will be recruited to participate. Small to medium size villages ranging between 200-500 people will be recruited; per our power analysis, we require 7 villages per arm and ~100 children who are ≤10 years of age per cluster.

Recruitment will follow the procedures performed during RIMDAMAL I, whereby prospective areas in Southwest Burkina Faso from which villages could be recruited will be identified by consultations between the IRSS regional director (Dr. Dabire) and scientists, and the national and regional health authorities at the Burkina Faso MoH. Primary considerations will be whether or not SMC is ongoing in the prospective areas, whether other scientific or clinical studies in the prospective areas are planned or ongoing, and whether other malaria control and/or NTD control interventions (e.g. IRS, MDA with albendazole or azithromycin) are planned or ongoing in the prospective areas.

Once an ideal study area is targeted for recruitment, we will obtain spatial maps and visit the area to understand the layout of villages, and make lists of ideal villages to recruit. We will attempt to choose villages that have distinct boundaries and non-populated buffer zones of agricultural fields or bush land surrounding them in order to minimize mosquito movement between control and intervention clusters and between study and non-study villages.

Subsequently, Dr. Dabire, other scientists of the IRSS, and regional health authority officers will approach the village chiefs, elders and CHWs, and describe the study to them and answer any questions they may have in an open meeting in the village. If these village leaders give their consent to proceed recruiting the village populace, a subsequent public meeting of all the heads-of-households in the village may be planned to again describe the study, and further answer any questions they may have. Upon gaining these community consents, randomization/allotment will occur at the public event described in section 5.3.1, and following that, screening and enrollment will begin.

7.2. Screening

Once community consent is affirmed and randomization/allotment occurs, screening, consent and enrollment will proceed with individual participants in each study village. The study investigators will travel to each village and meet publicly with the heads-of-households to re-inform them of the study goals and objectives, of the process of the public randomization event, and the intervention procedures that will occur with family members in their own households. These interventions include the data and sample collection procedures. The heads-of-households will be reminded of the need for them and their family members to be present for any subsequent interventions in their village, and of the active case surveillance in any children of theirs which may be enrolled in the active case detection (ACD; referring to children who will be regularly checked for malaria cases/episodes by the clinical team) cohort.

The administration of the interventions will proceed at the beginning of the months designated by the regional health authorities for SMC round administrations (July-October in each intervention phase season). As the intervention proceeds, if the status of any individual changes regarding their eligibility to is more standard participant in the intervention (e.g., an allergic response to the study drug is determined), this information will be recorded on the case report form and flagged for the subsequent IVM MDAs. In the case of pregnancy, since this is contra-indicated for IVM treatment, all women of possible child-bearing age (ages 12-45 or still not had menopause) will screened using a pregnancy urine rapid test (e.g. SD Bioline hCG) in the week prior to each IVM MDA, and if positive, they will be excluded from the MDA.

7.3. Enrollment/Baseline

All persons who live in each study village and who do not have a permanent disability or serious medical illness that prevents or impedes study participation and/or comprehension will be asked to enroll. Once a head-of-household signs his/her household consent document (appendix VII), the investigators will engage all the members of each household, take a census of the inhabitants, conduct a questionnaire of inhabitants, survey the houses, and enroll adults ≥18 years of age with their written consent. Enrollment of children between 12-17 years of age will also be gained by obtaining their written assent, and children <12 years of age by obtaining the written consent of their parent/guardian. All consents and assents will be obtained in the presence of a community witness, who will sign his or her name to these documents. Members of the study team will subsequently map the household and house locations in the village. Screening and participant information will be recorded on eCFRs on tablets, and individual participant exclusions/inclusions for participating in the intervention will be recorded (see 5.1).

7.3.1. PK/PD cohort

PK/PD cohort children will be chosen from one control and one intervention village, using the arm code so as not to break the blind. They will be subject to follow-up at an increased frequency. Enrollment criteria are otherwise as for the ACD cohort, with additional exclusion criteria of a 1) hemoglobin <7 g/dL (done by Hemocue or other instrument), and 2) use of concomitant medications (Section 6.6). The total number of participants in the PK/PD cohort is n=180 and participants will be age-stratified. Up to one individual may be enrolled from each age strata within the same household:

- 5-10yo (n=60, 30 from each village-arm)
- 11-18yo (n=60, 30 from each village-arm)
- ≥19yo (n=60, 30 from each village-arm)

7.4. Follow-up

Active case surveillance will be conducted by study nurses visiting each enrolled ACD cohort child weekly following the start of the first MDA and ending 30 days following the last MDA of the season. At each visit, the nurse will record patient information in the CRF, measure axillary temperature, take a blood sample (for the RDT, slide and filter paper) if indicated, and treat with AL if an uncomplicated malaria episode is confirmed by the RDT. Any other treatment (e.g., paracetamol) will be in consultation with the study physicians.

All episodes of malaria will be classified as uncomplicated or complicated based on the following criteria:

Uncomplicated malaria (all the following must be present)

1) Fever (> 37.5°C) or history of fever in the previous 24 hours

2) Positive RDT

3) Absence of complicated malaria

Complicated malaria (any of the following)

1) Evidence of severe malaria (see Appendix D) and parasitemia

2) Parasite density > 500,000/µL*

* Note that clinical decisions are made by RDT. However, if a nurse/doctor requests a blood smear to be read urgently, this will be performed. If the parasite density is above this threshold in this instance, the participant will be treated as having severe malaria.

During these visits, the nurse will inquire about, and record in the CRF, any AEs spontaneously communicated by the rest of the enrolled village populace (passive surveillance), and treat them as able in consultation with the study physicians or refer them to the district health clinic or hospital. Complicated malaria or other SAE will be referred to the district hospital immediately. Interim safety and efficacy analyses will be performed in the middle of season 1 (between the 2nd MDA and the 3rd MDA) and in between the two intervention phase seasons, and presented to the DSMB as described in 9.5.

In addition to the active case surveillance by the study nurses, entomology teams will periodically sample mosquitoes from households in the village during each season, and members of the parasitology team or the nurses will take a finger blood sample from all cohort children and a subset of enrolled adult participants at cross-sectional time points each season.

7.4.1. PK/PD cohort

Participants in the PK/PD cohort will be subject to PK sampling during a single month either season over the course of the study. During that month, for enrolled participants, each of the three IVM doses will be directly observed. Small volume capillary blood samples (≤0.5mL) will be taken to determine IVM plasma concentration at up to 5 time points following the last dose of IVM. Participants will be visited on days 0 (day of 1st dose of IVM), day 1, and 2 to observe IVM dosing. PK sampling will occur at selected time points on up to 5 additional days (day 2, 3, 4, 7, 14, 21, and 28).

7.5. Final Study Visit

The active case surveillance final study visit of the intervention phase will occur 30 days following the final IVM MDA in season 2, approximately in November. On this visit, members of the parasitology team or the nurses will take a finger blood sample from all cohort children and a cross-sectional blood sample from subset of enrolled adult participants. Additional follow-up will occur for pregnancy follow-up

7.6. Early Termination Visit (if needed)

No early termination visits will occur if early termination is required or requested by a participant.

7.7. Unscheduled Visit (if needed)

All participants will be encouraged to directly contact their assigned nurse or the field physician regarding any health emergencies or consultations at any time during the intervention phase each rainy season by mobile phone supplied to the CHW stationed in each village. During unscheduled visits, the nurse will record patient information in the CRF and diagnose and treat any simple AEs as able under the consultation of the study physicians and/or refer the participant to the district health clinic or hospital. If a participant is found to meet the case definition of malaria during this visit, a blood smear and filter paper will be collected.

7.8. Additional Sampling

SAMPLES WILL ALSO BE OBTAINED AT ADDITIONAL TIMEPOINTS IN A SUBSET OF PARTICIPANTS--ALL CROSS-SECTIONAL HOUSEHOLDS AND SELECT OTHERS--IN ORDER TO OBTAIN A BASELINE ESTIMATE FOR PREVALENCE ESTIMATES. THESE FINGER PRICK BLOOD SAMPLES WILL BE COLLECTED DURING THE DRY SEASONS IN 2020 AND 2021, DURING THE WET SEASON IN 2021 AND AT UP TO 4 OTHER TIMEPOINTS THROUGHOUT THE YEAR. BLOOD SAMPLES WILL BE DRAWN VIA FINGER PRICK AND WILL BE PRESERVED ON SLIDES AND FILTER PAPERS FOR LATER ANALYSIS. BASELINE SAMPLES WILL ALLOW FOR BETTER ASSESSMENT OF CHANGES OCCURRING WITH IVM AND SMC DRUG PRESSURE. THIS ADDITIONAL SAMPLING WILL UTILIZE A SEPARATE INFORMATION SHEET AND CONSENT DOCUMENT. ONLY PARTICIPANTS WHO CONSENT TO PARTICIPATE IN THE ADDITIONAL SAMPLING WILL DO SO. STUDY PROCEDURES/EVALUATIONS

7.9. Clinical Evaluations

Clinical evaluations during active case surveillance will be specific to looking for signs and symptoms of uncomplicated malaria; specifically: 1) fever or history of fever in the previous 24 hours and 2) a positive malaria rapid diagnostic test. Signs and symptoms of complicated (serious) malaria (as listed in Appendix D) will also be assessed. AEs reported to the clinical team will be assessed for their seriousness, intensity, and causality related to the intervention by the field physician. Known common side effects from IVM MDA such as pruritis, dizziness, diarrhea or vomiting will be evaluated and treated according WHO guidelines (Appendix B), and the nurse will consult with the field physician if a full clinical evaluation or referral should be performed.

7.10. Laboratory Evaluations

7.10.1. Clinical Laboratory Evaluations

No pre-specified formal clinical laboratory evaluations will occur during the intervention phase of the trial, other than in the PK/PD cohort. Rather, only field tests with RDTs will be performed, and blood samples taken for later analyses that will occur between the 2 rainy seasons or after the intervention phase. RDTs for parasite infection to diagnose malaria episodes will be used by nurses in the field, as will urine RDTs to determine pregnancy status in women 12-45 years of age (and those not yet reaching menopause) in the week prior to each IVM MDA. Blood smears taken by nurses and the parasitology team will be stored for later staining and counting of asexual parasites and species by trained parasitologists. Blood smears will only be read urgently when advised by the clinical team to rule out severe malaria.

7.10.1.1. PK/PD cohort

Participants in the PK/PD will be subject to capillary PK sampling up to 5 time points from the following sampling times 0 (pre-last dose), 1, 4, 8, 12, 24, 48, 52, 60, 72 hours, and on day 7, 14, 21, and 28. At up to 3 time points, simultaneous capillary and venous samples will be taken to assess the correlation between concentrations in these matrices, enabling us to compare our data with previous studies, and inform our mosquito-based studies. Clinical laboratory safety monitoring (5 mL venous draw) will also be conducted on days 0 (pre-IVM), day 14, and day 28 in all PK/PD participants, which will entail a complete blood count (CBC) with differential, liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), and creatinine (Cr).

7.10.1.2. Instructions for Specimen Preparation, Handling, and Storage

Capillary blood from participants will be obtained by study nurses wearing disposable gloves, and by first wiping down the participant's finger using an alcohol wipe, and using a sterile, single-use lancet. Nurses handling patient blood will follow safety guideline SOPs and training for handling potentially-infectious human blood and body fluids. Dried blood spots and blood slide smears will be taken during ACD by study nurses will be labeled with the appropriate date and participant ID, and will be stored in their backpacks and slide cases until they return from the field. Upon return, the nurses will store the blood spots in designated containers at the field station, and fix and stain the blood slides following a SOP to be written by the parasitology team. The stained slides will then be transferred to the parasitology

laboratory monthly by car at the IRSS for subsequent examination and dried blood spots will be stored at -20°C for later molecular analyses.

These participant samples will be retained at the IRSS and/or at laboratories in the U.S or the Netherlands for further tests. Consent for the future use of these coded specimens is written into the ICFs.

Capillary and venous samples taken from the PK-PD cohort will be used to assess the correlation between concentrations in the time and compartment matrices. Samples will be placed on ice and centrifuged, plasma stored at-80°C, and shipped to Yale on dry ice. IVM will be quantified using an Agilent 6550 Quadrupole LC/MS/MS that is coupled in line to an Agilent 1290 Infinity LC system. Blood fed mosquito samples collected from the same participant's house will be similarly frozen individually at -80°C and ship them to CSU for subsequent analysis. The presence of IVM in blood meals will be determined using a derivatization + HPLC-fluorescence method. Additionally, a subset capillary blood spots representing those sleeping in each sampling house, and mosquito blood meals from that house will be profiled using DNA fingerprinting analysis. Data will be analyzed to determine if certain individuals/demographic strata (e.g. age groups and sex) receive more bites than expected over time, and how this relates to their IVM plasma concentration.

Clinical labs (CBC, AST, ALT, and Cr) will be collected in appropriate vacutainers and analyzed at the central IRSS laboratory.

7.10.1.3. Specimen Shipment

These samples will be coded according to the participants study ID and time-stamped and signed. They will be maintained and tracked by the study pharmacologist in a specimen-tracking log, including details on tracking shipments from Burkina Faso to the laboratories in the U.S and the Netherlands.

8. ASSESSMENT OF SAFETY

8.1. Definitions

Adverse Event (AE): (ICH) E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs, will be captured on the appropriate data collection form. Information to be collected for AEs includes event description, date of onset, an assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis), date of resolution, seriousness, and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an unsolicited AE. However, if the severity or frequency of any pre-existing medical condition increases, it will be recorded as an unsolicited AE.

If an event meets both the criteria of a study endpoint and an adverse event, the event will be reported either as a study endpoint or as an adverse event (not both).

Serious Adverse Event (SAE): An AE is considered “serious” if, in the view of either the site principal investigator or sponsor, it results in any of the following outcomes:

- Death,
- A **life-threatening AE**: An AE is considered “life-threatening” if, in the view of either the site principal investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or

- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note: Medical judgment should be exercised in deciding whether an adverse event should be classified as serious in other situations. Important adverse events are not immediately life-threatening or do not result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

8.2. Adverse Events Grading

All AEs (laboratory and clinical symptoms) will be graded for severity and assessed for relationship to study product (see definitions). AEs will be graded initially by the study team on-site, typically the nurse and/or study physician, and final grading of AEs will occur in consultation with Dr. Parikh. AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection form. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

8.2.1. Severity of Event:

Severity will be determined following the definitions set forth in the standardized grading of adverse events (NIH Division of AIDS Adult and Pediatric Toxicity Tables, November 2014, version 2.0; see: https://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf). Use of these standardized guidelines will allow for uniform reporting. The grades are defined as follows:

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Potentially Life-threatening AE
- Grade 5: Death

Changes in the severity of an AE should be documented to allow for assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

8.2.2. Relationship to Study Product:

The assessment of the relationship of an AE to the administration of study product is made only by those with the training and authority to make a diagnosis based on all available information at the time of the completion of the case record form. Whether the AE is related or not, is not a factor in determining what is or is not reported in this trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. In a clinical trial, the study product must always be suspect. To help assess, the following general guidelines are used:

- Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

The physician-investigators will use clinical judgment to determine the relationship with more specific objective criteria. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The physician-investigators will also consult the drug information and the DSMB as needed in the determination of their assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event prior to transmission of the SAE report to CSU, Yale, IRSS and DMID. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE case report form accordingly.

8.3. Management and Reporting of AEs

AE monitoring will occur both actively and passively. All AE will be graded and analyzed by seriousness, intensity and causality. AE monitoring in this study is crucial to properly weigh the potential benefits vs. potential risks of the study.

- In the entire enrolled populace, passive monitoring of AEs will occur through spontaneous reporting of events to the study clinical team, and recorded on CRFs. AEs will be recorded from the entire

enrolled populace, regardless if they were treated with ivermectin/placebo or not eligible to take the intervention. AEs will also be actively monitored on the days of distribution of ivermectin/placebo through direct questioning of AEs and recording on CRFs by study nurses. AE will be recorded over the intervention period occurring during 1st and 2nd rainy seasons. More specifically, AEs will be recorded from the start of the first MDA of each rainy season to 1 month after the last MDA of that season.

- For those children enrolled in the active case detection cohort, where children are visited weekly to assess for malaria incidence, active monitoring of AEs will occur through direct questioning of AEs by the study team. Additionally, passive monitoring of AEs will occur by participants spontaneously reporting directly to the nurses when the nurses are in the villages performing active case detection of malaria in the child cohort, or spontaneously reporting indirectly to the nurses via communication through the village community health worker (who will then communicate the AE directly to the nurse or field physician).
- For women that become pregnant during the intervention period, from the time of 1st intervention to 1 month after the last intervention for each rainy season, monitoring for birth outcomes will be conducted.

Participants who develop common AEs that possibly were a consequence of ivermectin treatment will be identified at follow-up visits and treated by the study nurses according to WHO guidelines for treating common AEs that occur from MDAs (see appendix B) as well as standard approaches in Burkina Faso. All adverse events will be noted in the participant's CRF.

In the case of mild AE, no further action will be taken by study staff except in the case of vomiting, in which case the study medication may need to be re-administered. AEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic. These will be collated from CRFs by the field physician and study data managers in the 4th week following each IVM MDA and reported to the PIs prior to the administration of the next IVM MDA.

8.3.1. Serious Adverse Events

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology.
- Recorded on the appropriate SAE data collection form.

- Followed through resolution.
- Reviewed and evaluated by the DSMB (periodic review unless related), DMID, and the IRB.

In the case of any SAE, subjects will be referred to the district hospital for management. Transportation to the hospital will be provided. All hospitalized participants will undergo record review to identify potential adverse consequences of study participation.

At any time after protocol follow up period or completion of this study, if the site principal investigator or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the site principal investigator or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

All SAEs will be reported to the DMID (see below), to the Physician-PI (Dr. Parikh) and to the in-country investigator (Dr. Dabiré), or their assigned representatives, within 24 hours of the nursing staff becoming aware of it via mobile phone or electronically. The SAE form in the CRF will ask for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible study clinician should ultimately assign the causality of the event.

AEs that are serious or unexpected and are at least 'possibly related' to the intervention require expedited reporting within 24 hours of nurse becoming aware of it, and reporting within 24 hours to the sponsor by the country investigator or assigned representative becoming aware of it (e-mail notification); i.e. this will be a maximum of 48 hours after the field nurse becomes aware of it (including the 24 hours required for the field staff to report to the country investigator / representative). The DMID will report all SAEs to the DSMB. Additional information will be sent within 14 additional days (full SAE report) if the reaction had not resolved at the time of e-mail notification.

Table 5: Reporting of Adverse Events

Institution	Type of Adverse Events	When to Report
• **Yale-HIC** • **CSU IRB** • **IRSS/Centre Muraz**	• Related and Not Related to participation in the research **AND** Serious **OR** Unexpected (in terms of nature, specificity, severity, or frequency)	• Within 5 days of awareness • Related Events not meeting prompt reporting requirements are reportable in summary form at time of continuing review

DMID Pharmacovigilance Group¥	• All Serious Adverse Events (as defined in 9.1)	• Within 24 hours

¥All SAEs must be submitted within 24 hours of site awareness on an SAE form to the DMID pharmacovigilance contractor, at the following address:

DMID Pharmacovigilance Group

Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650

Bethesda, MD 20817, USA

SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)

SAE FAX Phone Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)

SAE Email Address: PVG@dmidcroms.com

The DMID Medical Monitor and DMID Clinical Project Manager will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID Medical Monitor will review and assess the SAE for potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the Principal Investigator or appropriate co-investigator becomes aware of an SAE that is suspected to be related to study product, the Principal Investigator or appropriate co-investigator will report the event to the Sponsor and the DMID Pharmacovigilance Group.

8.3.2. Reporting of Pregnancy

Pregnancies communicated by any participants to the clinical team, or discovered by the clinical team with the use of screening by urine RDT pregnancy tests prior to each IVM MDA, will be noted on the participant's CRF. The CRF indicator will then be used to identify these participants as not being eligible for receiving the intervention (IVM or placebo). The pregnancy status of these individuals will not be reported to the IRBs, sponsor, or regulatory agencies.

Enrolled women that become pregnant during the intervention period, from the time of 1st intervention to 1 month after the last intervention for each rainy season, monitoring for birth outcomes will be conducted.

8.4. Halting Rules

Interpretation of results and decisions about discontinuation of any treatment arms will be made by the DSMB, using the suggested guidelines given here. We do not propose that the DSMB be strictly bound by pre-specified criteria, because of the complexity of the trade-offs between safety, efficacy, and costs of the intervention, and the possibility that new information from contemporaneous ivermectin trials will change considerations. Rather, consideration of stopping guidelines requires a reasoned judgment based on all information that is available at the time of data review. As this is a double-blind, placebo-controlled study that uses malaria incidence as the primary outcome, it will not be possible to accurately-measure the expected, modeled effect size (Figure 4, ~43%) until the end of the second treatment season (after MDA 8). Therefore, interim analysis of superiority of effect size in one blinded arm over the other will not be available in an appropriate timeframe to stop the study over the course of the two-year intervention. Furthermore, important secondary outcomes that ideally need 2 season of intervention are designed to determine if repeated ivermectin MDA treatment affects ACT resistance in malaria parasites and the possible development of ivermectin resistance in mosquitoes.

Instead, the interim analyses of safety (AEs) , relative to the expected benefits in possible reduced malaria incidence in the cohort and reduced NTD among the treated populace, will provide the main data points for consideration of early halting of the trial. The expected AE incidence of the present study can be estimated from the RIMDAMAL I and IVERMAL trials, and used to decide if drug-related AE incidence is abnormally high relative to the expected benefit. The RIMDAMAL I trial had a dosing regimen of 150-200 µg/kg every 3 weeks for 18 weeks (6 treatments) to eligible participants in villages of the same region as this study. This resulted in AE being observed in 3% of the entire population of the study arm (45 AE in 1447 participants). However only ~75% of these participants were repeatedly treated with drug in the arm, and only 5 of these AE were considered possibly or probably related to the intervention (5/787 treated participants; 0.6%). All were classified as standard AE (see Appendix B) of mild or moderate intensity that consisted of vomiting, pruritus, edema in the limbs, or tremors. In the IVERMAL trial, 48 adult participants with confirmed symptomatic uncomplicated *Plasmodium falciparum* malaria were treated with one dose of an ivermectin regimen consisting of 3 days of 300 µg/kg/day that was co-administered with a 3-day course of dihydroartemisinin-piperaquine. This resulted in 8% (4/48) participants having an AE, but only 4% (2/48) of which were considered treatment-related. These AE were minor visual disturbances. Neither trial observed any treatment-related SAE.

Each round of MDA is given to the entire study population over the course of 3 days. Data on AEs/SAEs will accumulate over the course of the month following each MDA, and data will be entered into the eCRFs. Thus, the data at the end of each round of MDA should capture all enrolled individuals by either active or passive follow-up. The study team will review these data on an ongoing basis for any concerning safety signals. It is anticipated that the first full safety review of the initial round of MDA will

occur around between the 2nd and 3rd MDA round due to the time it will take to input and collate data. At the time of this review, and all others, it is recommended that if treatment-related AEs (Grade 2 or above) occur in 10% of the treated participants in the intervention arm, or if treatment-related SAE occur in 2% of the treated participants in the intervention arm, the following will take place:

- The dose of IVM will be reduced to a 1x400 µg/kg dose (see section 6.3).
- The DSMB should immediately convene an ad-hoc meeting that considers both unblinded safety data, as well as efficacy data (modeled and actual effect size of the primary outcome), to consider whether the study should be halted early or continue with a 1x400 µg/kg dose.

The DSMB will have a scheduled meeting between the 2nd and 3rd MDA round, and after the completion of 1st rainy season. At this point, the DSMB will review all safety data to determine if dose modification is potentially warranted.

Following recommendation from the DSMB, the sponsor reserves the right to temporarily suspend 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 investigators. 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 DMID/NIH, the CSU and Yale IRBs and the Comité d'Ethique of the IRSS, and provide the reason for the suspension or termination. The study may also be suspended or terminated at the discretion of the DMID/NIH based on funding decisions.

8.5. Data and Safety Monitoring Board

Safety oversight will be conducted by a DSMB that is an independent group of experts that monitors subject safety and advises DMID. The DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to this trial. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial, and include a biostatistician, clinicians and scientists who are knowledgeable about malaria and field-based research in sub-Saharan Africa, and persons knowledgeable in the conduct of clinical trials.

The DSMB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB. Procedures for DSMB reviews/meetings will be defined in the charter. DSMB reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/SAEs. The DSMB will review SAEs on a regular basis and ad hoc during this trial. The DMID Medical Monitor will be responsible for reviewing SAEs in real time.

The DSMB will conduct the following reviews:

- The study's safety data will be analyzed by the DSMB after the interim analyses conducted after the 2nd MDA, and another conducted after the first full season of treatment.
- Ad hoc when a halting rule is met or DMID/DSMB chair may convene an ad hoc meeting if there are immediate concerns regarding observations during the course of this trial.
- Final review meeting: 6 to 8 months after clinical database lock to review the cumulative unblinded safety data for this trial. The data will be provided in a standard summary format. The DSMB may be asked to provide recommendations in response to questions posed by DMID.

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion, and may request the treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with the study intervention, and to continue, modify, or terminate this trial.

9. CLINICAL MONITORING

9.1. Site Monitoring Plan by CRO

During the intervention phase, trained clinical trial monitoring experts (e.g. ClimAfrica-CRO or another contract research organization [CRO]) will conduct at least six monitoring visits (before, during and immediately after the intervention phase of the study, each in rainy seasons 1 and 2). These will include assessment of site compliance and standard operating procedures, review of consents, assents, training documents, research/study approvals and data collection forms, review of site facilities, and laboratory sample storage, shipment, and labeling. The study monitor will collate and promptly share their reports with the study investigators and study sponsor. The investigators will provide these reports to the DMID for their assessments of the study's adherence to GCP practices and recommendations and/or considerations of early trial termination due to possible data quality or safety concerns.

10. STATISTICAL CONSIDERATIONS

10.1. Study Hypotheses

The primary objective hypothesis is that repeated IVM MDAs (the intervention) coinciding with SMC rounds and other standard-of-care malaria control measures (LLIN distribution, IPTp) will significantly reduce the incidence of childhood malaria compared to the placebo intervention. This hypothesis will be tested in a 2-arm superiority trial with a cluster randomized design. The primary outcome measures of incidence of malaria episodes among village children ≤ 10 years of age in each arm will be used to test the hypothesis. The primary objective null hypothesis is that that repeated IVM MDAs coinciding with SMC rounds and other standard-of-care malaria control measures will have no effect on the incidence of childhood malaria compared to placebo MDAs coinciding with SMC rounds and other standard-of-care malaria control measures.

Secondary objective hypotheses:

- The risk of adverse events (AEs) per participant in the intervention arm occurring over the intervention phase of the trial will not differ relative to the risk of adverse events in the control arm. *Null: The risk of adverse events (AEs) per participant in the intervention arm occurring over the intervention phase of the trial will not differ relative to the risk of adverse events in the control arm.*
- The survival rates of wild blood fed *Anopheles gambiae* s.l. will be significantly reduced, and age-structure and entomological inoculation rate in wild *Anopheles gambiae* s.l. significantly younger/lower, in those captured from intervention arm villages as compared to those captured control arm villages at equivalent time intervals during the intervention phase. Also, the immuno-reactivity of intervention-arm participants' IgG over time to an *Anopheles* salivary gland peptide will be significantly lower than than that from control arm participants. *Null: The survival rates of wild blood fed Anopheles gambiae* s.l.*, and parity and sporozoite rates in wild Anopheles gambiae* s.l.*, will not differ in those captured from intervention arm villages as compared to those captured control arm villages at equivalent time intervals during the intervention phase. Similarly, the immuno-reactivity of intervention-arm participants' IgG over time to an Anopheles salivary gland peptide will be no different than that from control arm participants.*
- The *Plasmodium falciparum* multiplicity of infection per episode or blood sample, and number of new *Plasmodium falciparum* clones per unit time per child, will be significantly reduced in intervention arm children compared to control arm children. *Null: The Plasmodium falciparum multiplicity of infection per episode or blood sample, and number of new Plasmodium falciparum*

clones per unit time per child, will not differ in intervention arm children compared to control arm children.

- The concentration of ivermectin in participant's plasma will change over time post-drug administration and vary between age and gender strata. Mosquitoes that feed on recent ivermectin-treated participants will have detectable ivermectin in their blood meals. *Null: The concentration of ivermectin in participant's plasma will not change over time post-drug administration and will not vary between age and gender strata. Mosquitoes that feed on recent ivermectin-treated participants will not have detectable ivermectin in their blood meals.*

10.2. Sample Size Considerations

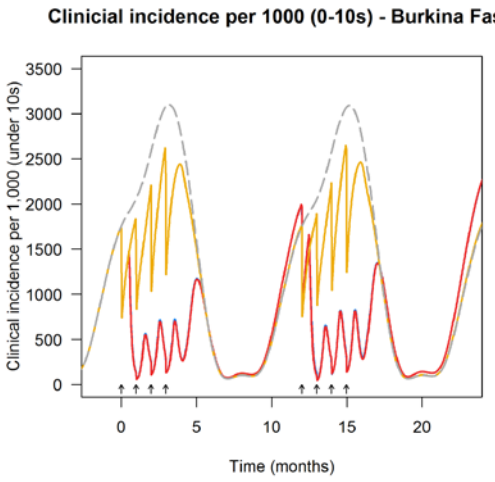
The trial design and power calculation is guided by the Malaria Transmission model developed at Imperial College, London (http://www.imperial.ac.uk/malaria-modelling/tools-and-data/) and informed by data from our RIMDAMAL I trial as well as the longer mosquitocidal effect (up to 30 days) from the intervention dose and regimen predicted from IVERMAL data. The model suggests we should observe an effect size in the intervention arm over the control arm of 43.1% (Figure 4). This assumes a rate incidence in our 0-10 yr. old cohort of 1.088 malaria episodes/child/year and 0.619 malaria episodes/child/year in the control and intervention arms, respectively. To determine the cluster sample size and cluster population (children cohort size) we used the sample size formula for obtaining the number of clusters in an unmatched CRT design with a 'rate' endpoint (49). The formula uses the coefficient of variation (κ; SD/mean) of the true rates between clusters within each group, which we estimated in southwestern Burkina Faso to be 0.258 (50). From these variables, and setting the α=0.05 (Type I error rate or probability of detecting a false negative result = 1.96), 6 clusters/arm with a minimum of 48 children/cluster in our child cohort is necessary to detect a significant difference in the rates between the arms with 80% power (Type II error rate or probability of rejecting a false positive result = 0.84). Relatedly, if we instead calculate the cluster population sample size using the intracluster correlation coefficient retrospectively calculated from RIMDAMAL I data (ICC=0.059), and setting the α=0.05, with 6 clusters/arm the necessary number of children to follow per cluster is 9.

In January 2019, the sample size modeling exercise was re-performed because it was learned that that villages in the Diebougou health district (the study site) were expected to receive new Interceptor G2 LLINs prior to the 2019 rainy season. These new LLINs are made with two different insecticides (chlorphenapyr and alpha-cypermethrin) to circumvent the prevalent pyrethroid-resistance seen in Burkina Faso the much of SSA. Thus, we assumed a 12%-50% reduction in malaria incidence in

both arms due to distribution of these nets. Keeping with an effect size of 43.1% in the intervention am over the control arm, using an intra-cluster coefficient of 0.2, and increasing the sample size to 100 children/cluster in our child cohort, we need between 4.9 and 5.5 clusters/arm to detect a significant difference in the rates between the arms with 80% power. Given that we will select 7 villages per arm, which are expected to have population sizes of 0-10 year old children of approximately 100, we feel we will have >80% power to reject the null hypothesis if it is false, even if some children drop out of the study or are lost to follow-up.

The primary outcome will be analyzed as intention-to-treat. The incidence of episodes from the children cohort will be used as the primary measurable outcome to evaluate the impact of the intervention when compared to the control arm. The primary analysis will use either cluster-level analyses, or multilevel/hierarchical regression modeling techniques to account for clustering at the level of the randomization unit (village), as well as analyze individuals with multiple time points. and comparisons using a critical value of α at 0.05. The analysis may need to be corrected to account for the relatively few number of clusters in the study design. The unadjusted as well as adjusted estimates depicting the impact of the intervention versus control will be reported along with 95% confidence intervals. The statistical programs R (r-project.org), SAS v9.4 (SAS Institute Inc., Cary, NC), or others will be used for the primary statistical analyses.

Figure 3: Modeling of the primary outcome when adding IVM MDA to SMC



Modeling of the primary outcome when adding IVM MDA to SMC. Clinical incidence in 0-10 year olds is predicted to drop by 54% in SMC+IVM MDA villages (red line) compared to no intervention (gray dotted line) and by 43% over those receiving the currently approved regimen of SMC alone (yellow line). Cases per 1000 0-10 yr. olds/yr are assumed to be 1351 with no intervention based on past data, and predicted to be 1088 with SMC alone but 619 with SMC+IVM MDA. Arrows on the X-axis denote each monthly treatment round.

10.3. Planned Interim Analyses

10.3.1. Interim Safety Review

AE risk data for each arm following the first MDA round will be accumulated and provided to the DSMB between the 2nd and 3rdMDAs, as well as following the entire first season of MDAs for safety analyses. The DSMB will review the AE compared between intervention and control arms by examining calculated risks ratios and attributable risks with 95% confidence intervals. Serious adverse events (SAE) will be similarly analyzed. The statistical program (e.g. R or SAS or others will be used for the AE statistical analyses. The DSMB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB. The frequency of DSMB meetings, the statistical techniques, rules

and recommendations for stopping guidelines based on AE rates and types, and the types of analyses expected for DSMB reviews/meetings will be defined in the charter.

10.4. Final Analysis Plan

The final statistical plan will be written in detail in the finalized standard operating procedure, f before the start of the intervention phase, to ensure that the sampling plan (e.g. number of nurse visits, number of mosquitoes and blood samples) collected are appropriate for the intended analyses. In general, standard, two-tailed statistical hypothesis testing α=0.05, as well as estimating and comparing the effect sizes and confidence intervals, will be used to measure the differences in entomological and parasitological secondary outcomes between arms. The tests used will depend on the type of data collected (e.g., survivorship of blood fed mosquitoes in each arm per collection interval, proportion of mosquitoes parous/arm per collection interval, average counts of trophozoites/slide or counts of the parasite molecular force of infection, sporozoite rates in mosquitoes), and their distributions. These data will also be used to make generalized linear and non-linear mixed effects models in R, SAS or other programs to understand the functional relationships of measured entomological and parasitological variables and the relative contributions of various independent variables on variation in the dependent variable.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

All CRFs containing participant demographic and clinical data (active case surveillance data on the children cohort and AE data for all participants) will be entered on password-protected tablets that will be maintained and updated daily by the clinical team working at the field site. This data will gathered in an electronic data capture system (e.g. REDCap) and be collated and sent encrypted over the internet to be entered into the study database managed by the study data manager(s). Data from participant blood smears will be kept on laboratory notebooks kept by the parasitological team at the IRSS in Burkina Faso, and entered in the same CRFs and study data base by the study data managers. Only the study team will have access to the source data. Long-term maintenance of the participant codes will be held only by the study PIs on password-protected computers and files.

We will permit authorized representatives of the sponsor(s), DMID, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

12. QUALITY CONTROL AND QUALITY ASSURANCE

A detailed quality management plan will be written before the start of the intervention phase of the trial that is in accordance with DMIP guidelines for assuring the quality of the research being conducted. This plan will have standard operating procedures (SOPs) for quality management which describe how the data will be evaluated for compliance with the protocol and for accuracy in relation to source documents. How the documents will be reviewed (e.g., CRFs, notes, product accountability), who is responsible for the reviews, and the frequency for reviews. Methods of training for staff will also be outlined in SOPs and the staff will need to sign off on each training they receive.

The study monitor (CliMAfrica-CRO or other) will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH/GCP guidelines, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to the investigators, the sponsor, and the DMID.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1. Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

The trial will also be conducted in compliance with the principles of the Declaration of Helsinki (1996) (http://www.wma.net/en/30publications/10policies/b3/), the principles of ICH-GCP, and in accordance with all applicable regulatory requirements by Agence Nationale de Régulation Pharmaceutique (ANRP) within the Burkina Faso Ministry of Health.

The principal investigators and other key personnel have no competing interests or conflicts of interest for the overall trial.

13.2. Institutional Review Board

This protocol, the informed consent documents, and participant case report forms will be reviewed and approved by the IRBs at Colorado State University, Yale University, and the Comité d'Ethique d'IRSS. Any amendments to the protocol or consent materials must also be approved before they are placed into use.

Each site principal investigator will obtain IRB approval for this protocol to be conducted at his/her research site(s), and send supporting documentation to the DMID before initiating recruitment of subjects. The investigator will submit applicable information to the IRB/IEC on which it relies for the review, to conduct the review in accordance with 45 CFR 46, ICH E6 GCP, and as applicable, 21 CFR 56 (Institutional Review Boards) and 21 CFR 50 (Protection of Human Subjects), other federal, state, and local regulations. DMID must receive the documentation that verifies IRB/IEC-approval for this protocol, associated informed consent documents, and upon request any recruitment material and handouts or surveys intended for the subjects, prior to the recruitment and enrollment of subjects.

Any amendments to the protocol or consent materials will be approved by the IRB/IEC before they are implemented. IRB/IEC review and approval will occur at least annually throughout the enrollment and

follow-up of subjects, and may cease if annual review is no longer required by applicable regulations. The investigator will notify the IRB/IEC of deviations from the protocol and reportable SAEs, as applicable to the IRB/IEC policy.

Each institution engaged in this research will hold a current Federalwide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research.

A single IRB of record, Colorado State University IRB, will be accountable for compliance with regulatory requirements for this multi-centered study. The SMART IRB reliance agreement in accordance with NIH policies will government the agreement between the CSU and Yale IRBs. Participating sites will then rely on the IRB of record to satisfy the regulatory requirements relevant to the IRB review. The participating sites will maintain essential required documentation of IRB reviews, approvals, and correspondence, and must provide copies of any agreements and essential documentation to the DMID or regulatory authorities upon request.

The IRB/IEC will determine that adequate provisions are made for soliciting the permission of each child's parent(s) or legal guardian, including whether permission of one parent is sufficient for research or whether permission is to be obtained from both parents. The IRB/IEC will determine how consent from subjects will be obtained when participation in the study is ongoing, and the subject has reached the age of majority.

13.3. Informed Consent Process

Community consent/assent (oral) will first be obtained by public meetings with local village chiefs and elders during the recruitment phase where the study will be explained to them. Following this, in the enrollment period, individual consent/assent (oral) through a public meeting with village heads-of-households will be obtained and at the end of the meeting written informed consent will be obtained from each head-of-household who chooses to have their family participate. Lastly, witnessed informed consent will be obtain from each person in orally-consented households by going door-to-door to households. The informed consent discussion will be in the appropriate language for the adult or the parents/guardians; translators will be used if necessary. The study information sheet given to each head-of-household will be written in French, as well as local languages predominately spoken in the region. Written, informed consent from each head-of-household will be in French and verbally translated into the appropriate language for the adult or the parents/guardians by translators. If the parent/guardian/participant is unable to read or write, their fingerprint will substitute for a signature, and a signature from a witness to the informed consent procedures will be obtained. The witness may be a family member, clinic staff not conducting the informed consent discussions, or a translator. The

consent process shall be initiated at the time of enrollment into the study and shall continue throughout the patient's participation.

Participants will receive an explanation that the trial involves research, and a detailed summary of the proposed study procedures and study interventions/products. This will include aspects of the trial that are experimental, the probability for random assignment to treatment groups, any expected benefits, all possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant, that are currently unforeseeable), the expected duration of the subject's participation in the trial.

Subjects will be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. Subjects will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. They will be informed of whom to contact (e.g., the investigator) for answers to any questions relating to the research project.

Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. The subjects will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled.

The extent of the confidentiality of the subjects' records will be defined, and subjects will be informed that applicable data protection legislation will be followed. Subjects will be informed that the monitor(s), auditors(s), IRB, NIAID, and regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form, the subject is authorizing such access.

Subjects will be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the subject's identity will remain confidential. Subjects will be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Subjects will be allowed sufficient time to consider participation in this research trial, and have the opportunity to discuss this trial with their family, friends or legally authorized representative, or think about it prior to agreeing to participate.

Considering the villages are populated by many illiterate participants, an independent witness will be present during the informed consent process and will sign the consent form as a witness, while the participant will be asked to indicate consent or assent by use of thumbprint. Any participant may withdraw their consent at any time throughout the course of the study, and this will be made clear in the informed consent process. All individuals will be informed that there is no requirement to join the study and that the standard medical care they might have through the CHWs and the local health district will remain the same regardless of study enrollment.

In accordance with the IRSS Comité d'Ethique, the head-of-household will be given a study information sheet explaining the study, as well as a head-of-household consent statement to read and sign. All adults will be asked to read the consent for (or if illiterate, be read the consent form) and sign an adult consent form.

13.3.1. Informed Consent/Assent Process (in Case of a Minor)

Investigators will follow IRB/IEC requirements for enrollment of minors in this study. Minors will be informed about the study to the extent understandable to the minor. Investigators or designee will conduct the consent process with the parent(s)/legal guardian, who will be given an IRB/IEC-approved permission form, which may be referred to as a consent form, to read, review, and sign prior to any study procedures. The parent(s)/legal guardian will be provided meaningful study information including a statement that this study involves research, the child may not benefit from the trial, and the study involves risk. The required elements will be clearly presented, including the purpose of the study, the experimental procedures, the potential risks and discomforts, known adverse effects, possible benefits of the study for the subject, alternative therapies that may be beneficial, use and disclosure of private information, and other elements that are part of obtaining proper consent. The subject's parent(s)/legal guardian will be allowed sufficient time to discuss questions with the investigator.

The investigator or designee will describe in simplified terms the details of the study intervention/product, study procedures, risks and discomforts, benefits, and other consent elements, as appropriate. A separate IRB/IEC-approved assent form will be used for the minor, who may read and sign the form, or have it read to him/her prior to participation in study procedures. Assent may be obtained verbally or waived when approved by the IRB/IEC as appropriate to age. If a child declines to participate in the trial when assent is required by the IRB/IEC, the subject will not be enrolled even though the parents have provided permission.

To ensure that consent is an ongoing process throughout the subject's participation in the study, the investigator and staff will review information as needed with the subject and the parent(s)/legal guardian and confirm that assent and permission are continuing. The permission and assent documents

will be updated when new information is acquired that may impact the decision to continue in the study, and the subject's assent and the parent(s)/legal guardian's permission will be obtained, as applicable.

The subject who reaches the age of majority will be consented at the next visit prior to study procedures. When no further visits are planned but the subject's participation is ongoing, the consent will be obtained via IRB/IEC-approved processes.

13.4. Exclusion of Women, Minorities, and Children (Special Populations)

To complete the aims and purpose of this study, we will attempt to enroll the entire populace of each village invited to participate. Thus, this study will not exclude any women, minorities or children, nor special populations, including illiterate or non-writing individuals.

13.5. Subject Confidentiality

Personal and medical information relating to research participants will be treated as confidential. The risk of disclosure will be minimized by secure storage of documents on password protected tablets and computers, and use of linked data by replacing personal identifiers with a unique study code to conceal the identity of the patient. The linked list will be destroyed 5 years following the publishing of the study results.

Tests for malaria will be reported to the parent/guardian of the participant at point of care, to relevant study staff and where appropriate will be recorded in the patients' medical record book in addition to study CRFs. All participant information will remain confidential to the extent allowed by law. Unique numerical identifiers will be used for data entry. All screening forms and case report forms will be kept in a secured location with access limited to authorized study staff. Unique numerical identifiers will be used for the computer-based data entry and blood samples. Publications will contain only aggregate data. No identifying information will be included.

13.6. Study Discontinuation

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the study subjects and assure appropriate therapy or follow-up for the subjects, as necessary. The investigator will provide a detailed written explanation of the termination to the IRB/IEC. If any subject's private information will continue to be collected for this study, the IRB/IEC must approve a consent form with the study procedures, any risks and discomforts,

and applicable elements, and the investigator or designee will re-consent the subjects as approved by the IRB/IEC.

13.7. Costs, Subject Compensation, and Research Related Injuries

There is no cost to subjects for the research tests, procedures, and study product while taking part in this trial. If it is determined by the site principal investigator that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control, and treat any complications from this trial.

13.8. Future Use of Stored Specimens and Data

The consent documents will contain language asking for participant's consent to use their blood samples for future studies that may help in the prevention of malaria. The consent states that we will store blood with a code that does not contain any unique identifiers in laboratories in the U.S. and Burkina Faso, and that we may share the test results on their samples with researchers at other organizations but we will not give them any names, addresses, or any information that could identify them or their household. Also, after the study period has ended, we will remove any means to link the sample them and their household, and we will not be able to find the samples connected to them.

14. DATA HANDLING AND RECORD KEEPING

The investigators are responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained.

DMID and/or it designee will provide guidance to investigators on making corrections to the source documents and eCRF.

14.1. Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the physician-PI (Dr. Parikh) or designee.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of Dr. Dabiré. During the study, the investigator must maintain complete and accurate documentation for the study.

The study site data manager and team, in conjunction with the study biostatistician (Dr. Rao) and the Colorado Clinical and Translational Sciences Institute (CCTSI), will serve to coordinate data entry, management and statistical analysis for this study and will be responsible for data management, quality review, analysis, and reporting of the study data.

All investigators on this study will have access to the final dataset.

14.2. Data Capture Methods

Participant demographic data and clinical data (including malaria episodes and AEs) and clinical laboratory data will be entered into eCRFs and downloaded into a 21 CFR Part 11-compliant Internet Data Entry System (IDES) approved by the IRBs. The data system will includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.3. Types of Data

Data for this study will include participant demographics, malaria episodes and their treatment, safety data (AEs and their characteristics and treatment), and laboratory (blood parasite prevalence and parasitemias)

14.4. Timing/Reports

Study monitor reports will be required at the beginning, middle and end of the intervention phase. Interim safety reports will be conducted and submitted after the 2nd MDA and between the 1st and 2nd seasons, and reviewed by the investigators and IRBs, the DMID and the DSMB. Data analyses and reports to the DSMB, sponsor and the DMID/NIH will begin following season 1 and continue until the end of the project period in Year 5. Care will be taking not to break the blind when performing analyses before the end of the intervention phase is complete.

14.5. Study Records Retention

Study documents will be retained for a minimum of 5 years after the close out of the study at the study site. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.6. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, or Good Clinical Practice (GCP) requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, section 5.1.1

5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site principal investigator and personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to the IRBs.

All protocol deviations, as defined above, must be addressed in study subject data collection forms. A completed copy of the Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site principal investigator and personnel are responsible for knowing and adhering to their IRB requirements.

15. PUBLICATION POLICY

Following completion of the study, we will to publish the results of this research in peer-reviewed scientific journals. Following the International Committee of Medical Journal Editors (ICMJE) member journals publication policy, this trial will be registered at ClinicalTrials.gov, which is sponsored by the National Library of Medicine. The trial will be registered on or before participant enrollment.

The PI and MPI must submit or have submitted for them to the National Library of Medicine's PubMed Central (http://www.ncbi.nlm.nih.gov/pmc/) an electronic version of their final, peer-reviewed manuscript describing the primary outcome upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

- NIH Public Access Policy, http://publicaccess.nih.gov/
- NIH Office of Extramural Research (OER) Grants and Funding, http://grants.nih.gov/grants/oer.htm

As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first subject. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. A delay of up to 2 years is available for trials that meet certain criteria and have applied for certification of delayed posting.

As part of the result posting a copy of this protocol (and its amendments) and a copy of the Statistical Analysis Plan will be posted on ClincialTrials.gov.

For this trial the responsible party is Dr. Foy, who will register the trial and post results.

The responsible party does not plan to request certification of delayed posting.

Refer to:

- Public Law 110-85, Section 801, Clinical Trial Databases
- 42CFR11

- NIH NOT-OD-16-149

The funder and sponsor of the study will have no role in, or authority over, the study design, data collection, data analysis, data interpretation, writing, or the decision to submit publications and reports from this study.

The PI (Dr. Foy) and MPI (Dr. Parikh) will consult together, and have final decisions over who is eligible for authorship on any publications stemming from this study. They will also decide together on how the full protocol is disseminated or published, and if and how participant-level data or statistical code will be shared with investigators or entities outside of the study team.

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