Evaluating the and feasibility of reactive targeted parasite elimination vs. reactive case detection, with and without reactive vector control, as a community level intervention in response to confirmed, passively identified index cases in Zambezi region, Namibia

Phase II of a two-phase study

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Abbreviations and Acronyms

ACT	Artemisinin-based combination therapy
AL	Artemether-lumefantrine
CHAI	Clinton Health Access Initiative
DBS	Dried blood spot
DOT	Directly observed therapy
DP	Dihydroartemisinin-piperaquine
DSMB	Data Safety and Monitoring Board
EA	Enumeration Area
ELISA	Enzyme-linked immunoabsorbent assay
GIS	Geographic information system
GPS	Global positioning system
HH	Household
HRP II	Histidine-rich protein II
HS RDT	Highly sensitive rapid diagnostic test
IRB	Institutional Review Board
IRS	Indoor residual spraying
ITN	Insecticide treated net
ITT	Intention to treat
LAMP	Loop-mediated isothermal amplification
LLIN	Long-lasting insecticide treated bed net
LSHTM	London School of Hygiene and Tropical Medicine
MoHSS	Ministry of Health and Social Services
MEI	Malaria Elimination Initiative
MRC	Multidisciplinary Research Centre
NVDCP	National Vector-borne Diseases Control Programme
PCR	Polymerase chain reaction
Pf	*Plasmodium falciparum*
PI	Principal Investigator
QTc	Corrected QT interval
RACD	Reactive case detection
RAVC	Reactive vector control
RDT	Rapid diagnostic test
SAE	Severe adverse event
SARN – RBM	Southern African Regional Network of Roll Back Malaria
SNP	Single nucleotide polymorphism
SOP	Standard operating procedures
SDSS	Spatial decision support system
SUSAR	Suspected unexpected severe adverse reaction
TPE	Targeted parasite elimination
UCSF	University of California, San Francisco
UNAM	University of Namibia

Definitions

Active surveillance: A strategy to detect and record cases of malaria within a community by conducting screening away from a health facility.

Case investigation: After a patient is diagnosed with malaria at a health facility, the patient is interviewed about his/her symptoms, recent travel, ITN use, and household IRS coverage.

Case, malaria: A person in whom, regardless of the presence or absence of clinical symptoms, malaria parasites have been confirmed by quality-controlled diagnosis.

Case, imported: A person in whom the origin of malaria infection can be traced to a known malarious area outside the country in which the case was diagnosed, generally classified based on travel history.

Case, local: A person in whom the origin of malaria infection cannot be traced to a known malarious area outside the country where the case was diagnosed, generally classified based on travel history and local epidemiology.

Case, index: A person diagnosed with malaria via rapid diagnostic test (RDT) or microscopy, whose infection is included in the passive surveillance system; the trigger for reactive case detection.

Coverage: The proportion of the targeted population reached by a given intervention. Also known as operational coverage.

Hotspot: A location of geographically clustered malaria where transmission is more intense.

Household: Any single or collection of permanent or semi-permanent dwelling structures acting as the primary residence for a person or group of people thatthat generally cook and eat together. Some households may include members who sleep in other dwelling structures within the same compound if the members are still dependent on the head of household in the main household.

Household resident: Any person who usually resides within a household or slept in that household for at least one night in the past four weeks.

Local epidemiology: The distribution and transmission of a disease within a defined area; the epidemiology of a disease can vary in different locations.

Neighbour: A person living adjacent to the household of an index case.

Passive surveillance: A system to detect and record malaria cases among patients who are diagnosed with malaria at health facilities.

Reactive case detection: An active surveillance strategy where people living with or near an index case are screened and treated for malaria, and may be interviewed about their travel history, ITN use, household IRS coverage, and previous malaria-like illness.

Reactive vector control: A response strategy where the household of an index case, as well as neighbouring households, receive IRS with a different insecticide after the index case is reported, regardless of whether spraying was already conducted pre-transmission; can be part of targeted parasite elimination.

Severe adverse event: An experience that results in (1) death during the study period, (2) a life-threatening experience (one that puts a participant at immediate risk of death at the time of the event), (3) inpatient hospitalization during the study period, (4) persistent or significant disability or incapacity, or (5) specific medical or surgical intervention to prevent one of the other serious outcomes listed above.

Spatial decision support system: A geographical information system (GIS)-based system that integrates a surveillance database, analytical models, graphical map display, tabular reporting, and expert knowledge. It provides a platform to support programmatic decision-making and spatially targeted approaches to disease control and elimination.

Suspected unexpected severe adverse reaction: An adverse drug reaction that is suspected of having a

causal relationship to the medication used in the research and is unexpected.

Target area: The index case household and surrounding households closest to the index case. At least 25 people should be enrolled in each target area, around each index case. The houses should be approached in order of their proximity to the index case household. Houses more than 500 m from the index case household should never be enrolled in the study.

Targeted Parasite Elimination: A strategy to eliminate malaria parasites in people and mosquitoes in malaria "hotspots," including administration of anti-malarial medication to communities with or without reactive targeted IRS.

Study Summary

Title	Evaluating the effectiveness and feasibility of reactive targeted parasite elimination (TPE) vs. reactive case detection (RACD), with and without reactive vector control (RAVC), as a community level intervention in response to confirmed, passively identified malaria index cases in Zambezi region, Namibia
Primary hypothesis	We hypothesise that cumulative incidence will be lower in areas that receive TPE versus RACD and in areas that receive RAVC versus no RAVC.
Study design	Cluster randomised controlled trial with a 2x2 factorial design.
Aims	**Primary aim**: To compare the impact of TPE versus RACD, and RAVC versus no RAVC, on incidence of confirmed, passively identified malaria cases. **Secondary aims** Effectiveness: 1) To compare the impact of each intervention package (TPE+/- RAVC, RACD +/- RAVC) on: a) Incidence, passively detected at health facilities b) Prevalence of infection, among all ages, as detected by LAMP c) Seroprevalence, among all ages, measured by ELISA Feasibility: 1. To compare operational coverage, and determine the feasibility of reaching 80% coverage, for each intervention package; 2. To compare safety of the intervention packages; 3. To compare the acceptability of the interventions, individually and as packages; 4. To compare the costs and cost-effectiveness of the interventions, individually and as packages; 5. To measure medication adherence in both TPE and RACD arms.
Study site	Western Zambezi region, Namibia, a pre-elimination malaria setting. Eleven health facilities and their catchment areas will be included. The population of the study site is approximately 35,381 people. The study intervention will take place in a subset of Enumeration Areas, or EAs (see below "Sample size"). Additional samples may be obtained from confirmed cases passively detected at health facilities outside of this region, to better characterize parasite genotypes as local versus imported.
Time frame	October 2015 – December 2017
Unit of randomisation	Enumeration areas (EAs) within catchment areas of 11 study health facilities will be randomized to one of four intervention arms: 1. RACD only 2.RACD with RAVC 3. TPE only 4.TPE with RAVC
Target area	The index case household and additional houses closest to the index case, within 500m. **TPE and RACD**: After the index case household, additional households will be enrolled, in order of distance from the index case, until at least 25 people have been enrolled. All households enrolled must be located within 500m of the index case household. If less than 25 people live within 500m of the index case, all those present and consenting will be enrolled. **RAVC**: The index case and six additional households will receive RAVC. Households

	will be approached in order of distance from the index case household. If any household is not home or refuses spraying, additional households will be approached to ensure seven total households, or all households within 500m of the index case household, receive RAVC.
Intervention	Each time a confirmed malaria case is detected by the passive surveillance system, it will be reported through a rapid reporting system and mapped. If that case is within a study EA a team including a nurse, a field investigator, and a driver will respond to the case. When appropriate an RAVC team will be dispatched to provide indoor residual spraying. The four intervention packages include: 1. RACD only – Testing people in the index case household and closest neighbors who consent using RDTs, treating everyone who tests positive; 2. RACD with RAVC – Testing people in the index case household and closest neighbors who consent using RDTs, treating everyone who tests positive, providing indoor residual spraying to index case and six closest consenting households within the Target Area; 3. TPE only – Treating people in the index case household and closest neighbors who consent; 4. TPE with RAVC – Treating people in the index case household and closest neighbours who consent, providing indoor residual spraying to index case and six closest consenting households within the Target Area.
Treatment	All index cases passively detected at health facilities, all subjects with a positive RDT, and all consenting residents of the TPE Target Area, will be treated with artemether lumefantrine (AL), in accordance with the first line malaria treatment in the MoHSS formulary. Those diagnosed with malaria by RDT will also be treated with a single low dose of primaquine, according to the malaria treatment guidelines of the MoHSS.
Indoor residual spraying (IRS)	The study area will receive pre-transmission season indoor residual spraying (IRS) as implemented by Ministry of Health and Social Services (MoHSS), where IRS and LLIN distribution are targeted rather than universal. In the study, when a new index case occurs in an enumeration area assigned to RAVC, the index case household and six closest, consenting households will receive IRS with Actellic CS.
Primary outcome	Incidence of confirmed, passively detected local malaria cases in each study arm, captured at study health facilities, that are reported via the rapid reporting system by enumeration area.
Secondary outcomes	• Prevalence of infection, among all age groups, as measured by LAMP • Seroprevalence of infection, among all age groups, as measured by ELISA • Coverage of the intervention. Case intervention coverage is the proportion of eligible cases investigated of the eligible cases reported in the Rapid Reporting System. For both RACD/TPE, the proportion of eligible participants enrolled per intervention up to 25 out of the number of eligible residents within 500 meters of the index case household up to 25 per intervention. For RACD, the proportion of the population living in the Target Area that receives a finger prick to test for malaria. For TPE, the proportion of participants that receive an initial dose of antimalarial drug (intention to treat analysis) per intervention up to 25 per intervention out of the number of eligible residents within 500 meters of the index case household up to 25 per intervention. For RAVC, proportion of targeted houses that receive IRS up to seven per intervention out of the

	number of households within 500 meters of the index case up to seven per intervention. • Index case household coverage. Proportion of eligible participants in the index household receiving the intervention out of the number of eligible residents of the index household • Number of serious adverse events (SAEs) related to antimalarial treatment or additional IRS. • Acceptance as evaluated by participation rate in each of the combinations of interventions and by qualitative assessment. • Costs per intervention episode, and per case averted. • Medication adherence, as measured by pill count.
Evaluation methods	The primary outcome measure is malaria incidence in each study arm, passively detected at health facilities and confirmed by RDT or slide. These data will be obtained through routine surveillance data from the MoHSS surveillance system, where cases are reported via tablet within 24 hours. These data will then be fed into the spatial decision support system (SDSS) to geo-locate them and support intervention planning. Other secondary outcome evaluation methods: 1) Prevalence and seroprevalence will be assessed through a cross sectional household survey in a sample of residents of all intervention EAs at study conclusion. RDTs will be conducted, DBS will be collected, an interview conducted, and molecular testing and serology performed. 2) Coverage of RACD or TPE in the target population will be measured by comparing number of participants receiving the intervention (up to 25 per intervention) to the baseline population data of residents within 500 meters of index case households (up to 25 per intervention) available from Phase I (Geographical reconnaissance study). 3) Serious adverse event (SAE) reports will be assessed during Pill Counts, and through spontaneous reports by participants. 4) Adherence will be assessed by a pill count follow-up in select Target Areas. 5) Costing and cost-effectiveness data will be collected during study implementation in 2017. 6) Acceptability will be assessed through quantitative measurement of trial participation and the endline survey, and through qualitative assessment in focus group discussions and key stakeholder interviews.
Sample size	The sample size is based on the number of EAs that experienced at least one incident case of malaria in the previous three malaria seasons (Jan 2012-May 2014). There are 102 EAs in the study area. Of the 102 EAs, incidence data are not yet available in 29. Additionally a further 19 had no cases in the previous 3 years. This leaves a remaining 56 EAs available for inclusion (total population 18,022). In order to have equal EA numbers in each arm we have included 56 total EAs, each of which will be randomized to one of the four intervention arms. The final EA list includes 14 EAs each for the 4 study arms. Population size is unequal across different potential EA sets, thus sample size for power calculations is based on an effective sample size adjusted for this variation. The current set of 56 EAs has a harmonic mean of 276 people in each EA, for a total effective sample size of 15,456. For the primary objectives, we hypothesize that introduction of RACD alone (control condition for this study) will result in an incidence of 25 per 1000 population per year compared to the current 33 per 1000

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<tr><td></td><td colspan="4">population per year rate observed with limited active follow up.

We hypothesize that TPE and RAVC will each be associated with a 50% reduction in annual malaria incidence compared to RACD only, and that the combination of TPE and RAVC will be associated with a 75% reduction compared to RACD only, assuming no interaction. With the above sample size and assumptions regarding effect size, this study has at least 80% power to detect the hypothesized differences between TPE versus RACD, RAVC versus no RAVC, and the combination of TPE and RAVC versus RACD only.

Incidence of confirmed, passively detected cases will be captured through the existing surveillance system, and those occurring in study EAs identified. Secondary outcome measures for infection prevalence and seroprevalence will be measured in an estimated 5,040 people in the endline cross sectional survey. Other secondary outcome measures will be captured among people enrolled for RACD or TPE activities over the course of the study.</td></tr>
<tr><td>Study Design</td><td colspan="2"></td><td colspan="2">TPE vs RACD arms</td></tr>
<tr><td></td><td colspan="2"></td><td>RACD (28 clusters):</td><td>TPE (28 clusters):</td></tr>
<tr><td></td><td rowspan="2">RAVC vs no RAVC arms</td><td>No RAVC (28 clusters):</td><td>RACD (14)</td><td>TPE (14)</td></tr>
<tr><td></td><td>RAVC (28 clusters):</td><td>RACD + RAVC (14)</td><td>TPE + RAVC (14)</td></tr>
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Key Personnel

Principal Investigators	
Davis Mumbengegwi, PhD Deputy Director, and Head of Division of Science, Technology and Innovation, Multidisciplinary Research Centre, University of Namibia Email: dmumbengegwi@unam.na Phone: +264 (0) 61-206-3908	Dr. Mumbengegwi will provide local oversight of the project, with a focus on data collection and laboratory procedures. He will ensure compliance with standard procedures, and contribute to study design, data analysis, and manuscript writing. He will co-supervise project staff with the Program Manager.
Michelle Hsiang, MD Deputy Lead, Operational Research, Malaria Elimination Initiative, Global Health Group Assistant Adjunct Professor, Pediatric Infectious Diseases, Dept of Pediatrics University of California, San Francisco Assistant Professor, Pediatric Infectious Diseases, Dept of Pediatrics, University of Texas Southwestern Medical Center Email: Michelle.Hsiang@UTSouthwestern.edu Phone: +1-415-595-5978	Dr. Hsiang will be responsible for general leadership and oversight of the project. She will lead study design, provide oversight of standard operating procedures in the field and laboratory, and lead data analysis and manuscript writing.
Roly Gosling, MD, PhD Associate Professor, Dept. of Epidemiology and Biostatistics Lead, Malaria Elimination Initiative, Global Health Group, University of California, San Francisco Email: Roly.Gosling@ucsf.edu Phone: +1-415-597-8114	Dr. Gosling will be responsible for oversight of the project, including study design, partner management, funder liaison, and manuscript preparation. He will align study activities with other Global Health Group supported activities in malaria elimination.
Jennifer Smith, PhD Postdoctoral Fellow Malaria Elimination Initiative, Global Health Group, University of California, San Francisco Email: Jennifer.Smith@ucsf.edu Phone: +1-415-597-9247	Dr. Smith will participate in study design, data collection management, data analysis (particularly with spatial analyses), and manuscript writing.
Immo Kleinschmidt, PhD Professor of Epidemiology, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine Email: immo.kleinschmidt@lshtm.ac.uk Phone: +44(0)20 7927	Dr. Kleinschmidt will lead targeted vector control aspects of the project, including experimental design, data collection, analysis, and manuscript preparation
Adam Bennett, PhD Networks Lead Malaria Elimination Initiative, Global Health Group, University of California, San Francisco Email: Adam.Bennett@ucsf.edu Phone Number: +1 415 597 4981	Dr. Bennett will participate in study design, data analysis (including spatial analysis), and manuscript writing.
Co-Investigators	
Petrina Uusiku, MD Chief Medical Officer, National Vector-borne Diseases Control Programme, Ministry of Health and Social Services Email: uusikup@nacop.net Phone: +264-811-462-707	Dr. Uusiku will support aspects of the project supported by the National Vector-borne Diseases Control Programme (NVDCP). She will provide input on study design, coordination, and manuscript preparation. She will ensure that study findings inform future program planning and implementation as indicated.
Stark Katokele, MSc Parasitologist, National Vector-borne Diseases Control Programme, Ministry of Health and Social Services	Mr. Katokele will support surveillance aspects of data collection. He will provide support to the Research Coordinator in her work with regional and district NVDCP

Email: katokeles@nacop.net Phone:+264-812-928-754	staff to ensure quality data collection. He will help the Research Coordinator troubleshoot when issues arise.
Ronnie Bock, PhD Senior Lecturer, Dept. of Biological Sciences University of Namibia Email: rbock@unam.na Phone: +264 (0) 61-206-3234	Dr. Bock will support data collection and laboratory procedures. He will assist with field and student supervision.
Kathryn Roberts, MPH Namibia Project and Research Coordinator, Malaria Elimination Initiative, Global Health Group, University of California, San Francisco Email: Kathryn.Roberts@ucsf.edu Phone: +264-81-277-4407	Based in Namibia, Ms. Roberts will oversee the fieldwork, co-supervise study staff, and manage partner communications. She will ensure that the goals and procedures of the study align with policies and guidelines of the Namibia Ministry of Health and Social Services. She will collaborate on study design, data collection, analysis, and manuscript preparation.
Lisa Prach, PhD, MPH Research Specialist Malaria Elimination Initiative, Global Health Group, University of California, San Francisco Email:Lisa.Prach@ucsf.edu Phone: +1-415-476-5929	Dr. Prach will support the field coordination of the clinical trial, including study tools, site supervision, data collection, analysis, and manuscript preparation. She will also lead the cross-sectional endline survey in 2017.
Oliver Medzihradsky, MD, MPH, MSc Research Fellow Division of Pediatric Infectious Diseases Department of Pediatrics, UCSF Email:olivermed@ucsf.edu Phone: +1-530-318-3273	Dr. Medzihradsky will lead the serology sub-study. He will also support the field coordination of clinical trial, the data safety monitoring board, and providing ongoing monitoring of adverse events.
Bryan Greenhouse, MD, MA Assistant Professor, Division of Infectious Diseases, Department of Medicine, University of California, San Francisco Email: bgreenhouse@medsfgh.ucsf.edu Phone: +1-415-206-8844	Dr. Greenhouse will lead genotyping and will work with Dr. Mumbengegwi and his lab to support other laboratory related aspects of the project including PCR and serology.
Collaborators	
Mi-suk Kang Dufour, PhD Assistant Professor Division of Prevention Science University of California, San Francisco Email: mi-suk.kangdufour@ucsf.edu Phone: +1-415-476-6287	Dr. Dufour will provide statistical support in the study design and analysis.
Maxwell Murphy Laboratory Coordinator Division of Infectious Diseases, Department of Medicine, University of California, San Francisco Email: Maxwell.Murphy@ucsf.edu Phone: +1- 707-364-7044	Mr. Murphy will support the coordination of laboratory related aspects of the study. Will provide trainings, help coordinate sample transport and storage, ordering of supplies, troubleshooting in the lab, and will perform assays as needed.
Kim Baltzell, MS, PhD Associate Professor - Department of Family Health Care Nursing, UCSF Phone: +1-415-215-7701 Email: kimberly.baltzell@ucsf.edu	Dr. Baltzell will support the study design and analysis of the qualitative acceptability study.
Bradley Didier, MPH Program Manager, Malaria Technical Support Clinton Health Access Initiative	Mr. Didier will support collaboration between the Global Health Group, the Ministry of Health and Social Services, and CHAI. He will provide guidance in study coordination, data collection, and input on data analysis, and translation of study findings into program planning and implementation, as indicated.

Zaahira Gani. MSc Project Manager, Novartis Foundation Email: zaahira.gani@novartis.com	Ms. Gani will support project implementation through protocol and strategy review, and facilitating the relationship between the study and the Foundation.
Michael Reddy Malaria – Vector Control Program Officer The Bill & Melinda Gates Foundation Michael.reddy@gatesfoundation.org	Mr. Reddy will support reactive vector control design, implementation, and review, and facilitate the relationship between the study and the Foundation.
Munyaradzi Tambo, MS Laboratory Technologist, University of Namibia Phone: +264-81-4349435 Email: munyaradzitambo@yahoo.com	Mr. Tambo will be responsible for running all the samples that are processed in Windhoek under the direction of Dr. Mumbengegwi.
Henry Ntuku, PhD Postdoctoral Fellow in Randomized Controlled Trial Implementation Katima Mulilo, Namibia	Dr. Ntuku will be responsible for technical oversight of trial implementation including protocol review, training, field supervision, data management, and analysis.
Smita Das Scientific Laboratory Associate PATH Email: SDas@path.org Phone: +1-206-285-3500	Ms. Das will coordinate the quantitative HRP II concentration assays running and analysis.

Partners and qualifications

The University of California (UCSF) Global Health Group, The University of Namibia (UNAM) Multidisciplinary Research Centre, The Ministry of Health and Social Services' (MoHSS) National Vector-borne Diseases Control Programme (NVDCP), the University of Texas Southwestern Medical Center (UTSW), the London School of Hygiene and Tropical Medicine (LSHTM), and the Clinton Health Access Initiative (CHAI)

collaborated on a project in the Ohangwena and Omusati regions of Namibia to evaluate reactive case detection (RACD) beginning in 2012. Building on this work, the partners will work together in Zambezi region to evaluate targeted parasite elimination (TPE) as a strategy to interrupt malaria transmission. The project includes two phases: Phase I focused on building surveillance and response capacity and understanding local malaria epidemiology; Phase II involves implementation and evaluation of the effectiveness and feasibility of TPE.

The expertise of NAMEP partner organizations is described below:

Malaria Elimination Initiative, Global Health Group, UCSF

The Global Health Group at UCSF is an 'action tank' dedicated to translating new approaches into large-scale action that improves the lives of millions of people. The UCSF Global Health Group's Malaria Elimination Initiative (MEI) believes that global eradication of malaria is possible within a generation. Working with partners at global, regional, and national levels, the MEI accelerates progress by conducting operational research to improve surveillance and response, determining the costs of elimination, and strengthening political and financial commitment to shrink the malaria map.

Multidisciplinary Research Centre, University of Namibia

The MRC at UNAM works to implements applied research activities in priority areas. In 2011, the MoHSS mandated UNAM to conduct operational research on the Ministry's behalf, to achieve the regional RBM network's objective of malaria elimination. The MRC is a research hub conducting collaborative research with partners from UNAM faculty and local, regional, and international partners. The MRC will serve as a sub-grantee, managing funds for in-country implementation, including hiring and managing project staff, and processing samples in their bio-molecular research laboratory.

National Vector-borne Diseases Control Programme, Ministry of Health and Social Services

The National Vector-borne Diseases Control Programme (NVDCP) is a unit of Namibia's Ministry of Health and Social Services (MoHSS). The NVDCP is tasked with addressing vector-borne illnesses, including malaria, through surveillance, environmental control measures, and outbreak response. The NVDCP will guide the project design to ensure MoHSS goals are addressed and new interventions are scalable. Regional NVDCP and project staff will work together in Zambezi region, helping lead the implementation of this project.

The University of Texas Southwestern

The University of Texas Southwestern (UTSW) Medical Center is a leading biomedical institution devoted to clinical care as well as multidisciplinary research and scientific training in both basic and clinical research. Through a grant from the Horchow Family Fund, is supporting study design, oversight, implementation, and analysis.

The London School of Hygiene & Tropical Medicine

The London School of Hygiene and Tropical Medicine is a world-leading centre for research and postgraduate education in public and global health. Their mission is to improve health and health equity in the UK and worldwide, working in partnership to achieve excellence in public and global health research, education and translation of knowledge into policy and practice. The Malaria Centre at the London School of Hygiene & Tropical Medicine develops tools, techniques, and knowledge about malaria, with a strong emphasis placed on translating research outcomes into practice, including diagnosis and treatment.

The Clinton Health Access Initiative

The Clinton Health Access Initiative (CHAI) works to improve markets for lifesaving medicines and diagnostics, lower the costs of treatments, and expand access to life-saving technologies – creating a sustainable model that can be owned and maintained by governments. In Namibia, CHAI has a long-standing relationship with the MoHSS and the NVDCP to support their malaria program. CHAI will contribute to protocol development, capacity building, implementation, and is a coordinating partner for the project.

University of the Witwatersrand

The University of the Witwatersrand is a multi-campus South African public research university situated in the northern areas of central Johannesburg. For this study, the University of Witswatersand will be supporting the implementation and evaluation of the Reactive Vector Control (RAVC) intervention and entomological monitoring.

PATH

PATH is an international, nonprofit global health organization, which drives transformative innovation to save lives and improve health, especially among women and children. PATH will perform quantitative HRP II assays for this study and will contribute to manuscript writing.

The Novartis Foundation

The Novartis Foundation, a private sector foundation, takes a strategic approach and works to create sustainable health service models and improve access to healthcare for those most in need, leveraging its on-the-ground experience and partnerships on projects addressing an unmet need bringing solutions to public health problems. The foundation explores innovative interventions and measurements to bring the world closer to the eventual goal of leprosy and malaria elimination. The Novartis Foundation is a partner as well as a funder, providing valuable input for project design and implementation based on extensive experience in malaria in the developing world.

The Bill and Melinda Gates Foundation

The Bill and Melinda Gates Foundation is the largest private foundation in the world. The primary aims of the foundation are, globally, to enhance healthcare and reduce extreme poverty. For this study, the Foundation will be supporting the evaluation of the Reactive Vector Control (RAVC) and entomological monitoring, through a grant to Wits University.

1. Background

1.1 Namibia Malaria Elimination Research Partnership (NAMEP)

As a result of successful malaria control efforts, Namibia, like many countries in southern Africa, is aiming for elimination by 2020.[1] The National Vector-borne Diseases Control Programme (NVDCP) of the Ministry of Health and Social Services (MoHSS) and the Southern African Regional Network of the Roll Back Malaria have

identified surveillance research and strengthening as key determinants for the future of malaria control and elimination in the region. The NVDCP has asked the University of Namibia (UNAM) to support its malaria elimination aims through operational research. UNAM is interested in leading such research and further developing its capacity to study malaria in the low transmission setting of Namibia. The University of California, San Francisco (UCSF), the London School of Hygiene and Tropical Medicine (LSHTM), and the Clinton Health Access Initiative (CHAI) are established partners of the NVDCP and UNAM, collaborating to build the evidence base for malaria elimination strategies and decision-making.

Beginning in 2012, the partners conducted malaria elimination research in the Ohangwena and Omusati regions of Namibia, including implementing reactive case detection (RACD). Building on this work, the NVDCP, UNAM, UCSF, LSHTM, CHAI, the Bill and Melinda Gates Foundation, and the Novartis Foundation worked together during Phase I of this project to build surveillance and response capacity and better understand the epidemiology of malaria in the region. In Phase II of the project these partners have built on the findings from Phase I to implement a randomized controlled trial comparing RACD, the current standard response to a passively detected malaria case, to targeted parasite elimination (TPE), or presumptive treatment without testing. Additionally, the study will evaluate whether reactive indoor residual spraying (IRS) in response to index cases, in conjunction with RACD or TPE, provides an additional benefit.

1.2 Malaria Elimination in Namibia

Namibia has experienced a tremendous decrease in reported malaria cases, from 538,512 cases in 2001 to 4,593 in 2013. Ongoing interventions, such IRS, LLIN distribution, and the introduction of rapid diagnostic tests (RDTs) and artemisinin combination therapy (ACT), have contributed to this decline. During the same period, malaria deaths decreased by 98 percent from 1,728 per year to 36, far surpassing targets to reduce malaria-related deaths by 50 percent. However, recently the success has stalled, with 15,692 cases and 61 deaths in 2014 and 12,045 cases and 43 deaths in 2015. In 2016, the MoHSS declared a malaria outbreak, with the final number of cases, to be released in 2017, expected to exceed any of the previous years. New strategies are needed to re-establish progress towards malaria elimination. This study will explore a promising new elimination strategy, TPE, to evaluate its effectiveness, and determine its operational feasibility, acceptability, and cost and cost effectiveness.

The path to malaria elimination must include a shift in focus, from reducing the clinical burden of malaria to interrupting transmission, from only focusing on symptomatic infections to including asymptomatic infections as a priority. Since malaria transmission is highly geographically heterogeneous, elimination activities must target hotspots or areas where the risk of future infection is highest. In the transition from control to elimination, real-time surveillance and rapid response are necessary to target hotspots with interventions to interrupt transmission.[2]

Reactive Case Detection

Reactive case detection (RACD), which includes testing and treatment around passively detected cases, is a recommended elimination strategy to identify secondary cases and hot spots.[3–5]However, RACD can be labour, time, and cost intensive, and misses people who are absent during screening or refuse to have their blood drawn.[3] Microscopy is being replaced by antigen-based RDTs that provide convenience, rapid results, and reduce the need to rely on microscopists, but have limited sensitivity to detect low parasite density and non-falciparum infections.[6,7] Polymerase chain reaction (PCR) offers markedly improved sensitivity, but requires hours of processing time, sophisticated technical skills, and expensive equipment. Loop mediated isothermal amplification (LAMP) offers the sensitivity of PCR and is easier to perform, but because samples must be analysed in a laboratory, its usefulness for community-level screening and treatment is limited. How to detect both symptomatic and asymptomatic infections in a field setting continues to present a challenge for malaria elimination.

Namibia's malaria guidelines include notification of cases within 24 hours via a rapid reporting system, investigation of all cases, conducting RACD at the community level, treatment of any positives, provision of

health education, and reporting of any additional RDT-detected malaria cases. However, currently, it is not possible to conduct RACD for each malaria case in Zambezi region because of the high malaria burden.

AA case-control evaluation of RACD in Engela, Oshikuku, and Outapi districts, in Namibia, asymptomatic infections were more likely to occur near the homes of passively detected index cases compared to randomly selected controls. Using highly sensitive LAMP testing, among case neighbourhoods 64 secondary cases were found among 1,518 people (4% positivity rate) versus only two secondary cases found among 1,129 people screened in control neighborhoods (0.18% positivity rate). RDTs detected only 24 of the 64 (38%) secondary cases that were later identified by LAMP, indicating that RDTs are not sensitive enough to identify all cases of malaria. This is likely because standard RDTs are designed to detect symptomatic illness, where people are likely to have a higher density of parasites, rather than to detect asymptomatic or low-density infections (Sturrock, unpublished).

UCSF's collaboration with the Swaziland National Malaria Control Programme and CHAI to evaluate RACD in Swaziland has yielded similar findings. RDTs were shown to detect about 20% of asymptomatic infections when compared to PCR as the gold standard. As in Namibia, infections clustered around households of index cases, with those living within 200 metres of the index case at higher risk than those living from 200-500 metres away. (Hsiang et al, in preparation)

1.3 Targeted Parasite Elimination

Given the limitations of RACD to identify low-density infections, the logistical challenges and cost associated with the screening process, presumptive treatment may be a more feasible and effective strategy to reduce and interrupt transmission in certain settings.

Targeted Parasite Elimination (TPE), a form of presumptive treatment, has been used successfully in China to overcome some of the weaknesses of RACD.[8]In a low transmission setting, only a small proportion of the population is at high risk of infection, therefore, only a small number of people need to be targeted. TPE targets remaining reservoirs of infection in low endemic settings by treating everyone at high risk, rather than rely on RDT results, which have been shown to miss infections. TPE can also include indoor residual spraying (IRS) targeted to homes in high risk locations. For presumptive treatment to be effective, mathematical modelling suggests that 80 - 90% of the population must be covered.[10] This is made easier by accurately targeting small, limited populations.

1.4 Reactive case detection vs. Targeted parasite elimination

TPE is a promising strategy, but evidence does not yet exist to prove its efficacy in Africa.[9] Questions remain about where to target TPE, what drugs to use, and whether drugs should be used alone or in combination with additional vector control. There are questions about the acceptability to the community, costs and cost effectiveness, operational feasibility, and the sustainability of the impact. The advantages, disadvantages, and uncertainties around reactive case detection versus TPE are summarized in Table 1.

Table 1. RACD vs TPE

		RACD	TPE
Rationale	Identification/treatment low-density infections	- Misses low density infections + Prophylactic effect in those treated, depending on half-life of medication used	+ Does not rely on insensitive diagnostics + May provide prophylactic effect to entire target population, depending on half-life of medication used
Effectiveness	Effectiveness to decrease transmission	? Not well established	? Not well established
Feasibility	Coverage of intervention	+/- High acceptability facilitates good coverage, but logistics of testing make high coverage challenging	? Ease of giving medication without testing may facilitate high coverage at first encounter
	Acceptability	+/- Acceptability high, but occasional refusals due to community dislike for	+/- Anticipate some refusals to take medication, but acceptability may be high due to previous

		blood tests	experience with malaria and knowledge of the medication's prophylactic effect
	Safety using ACT	+ Treatment of only test positive people is safe	+ Treatment of many asymptomatic people is likely to be safe
	Safety using additional IRS	+ Likely to be safe	+ Likely to be safe, no evidence to suggest increased toxicity when used with antimalarials
	Adherence to drug regimen	+ Adherence among persons with known infection likely to be good	- Adherence among persons without known infection may be poor without some sort of directly observed therapy + Adherence may be good if treatment course is simple and short, perceived risk of malaria is high, and prophylactic effect is understood
	Cost-effectiveness	? Cost and time necessary to only treat vs screen and treat has not been measured, but as TPE treats asymptomatic infections, a reservoir for infection, the cost per case averted may be lower.	? Relative cost-effectiveness compared to the standard of care (RACD) is not known.

1.5 Drug Administration

The goal of TPE is to treat community members presumptively to eliminate any existing reservoir of malaria infection. For this study, we use artemether-lumefantrine (AL or Coartem), an artemisinin-based combination therapy (ACT) that is the first line treatment for uncomplicated *Plasmodium falciparum* malaria in Namibia and has been approved for use in over 80 countries. AL has proven safe and effective against uncomplicated malaria.[10]

The transmission blocking potential for AL has been described.[11–13] In asymptomatic populations, it has been evaluated for presumptive treatment among children with severe anemia (monthly for three months)[14], and found to be safe but not effective at reducing individual malaria risk. It has also been evaluated for mass screening and treatment among individuals of all ages.[15,16] In these studies, AL was shown to be well tolerated and safe with no severe adverse events, but not effective for reducing malaria transmission. These studies were challenged by their high transmission settings, and the screening and treatment studies were additionally limited by the poor sensitivity of RDTs to detect low-density infections. The use of AL for focal presumptive treatment in a lower transmission setting such as Namibia, has a higher potential to be effective at transmission reduction.

AL dosing is weight adjusted, allowing for pediatric dosages (Appendix I). Regardless of age, the second dose is administered eight hours after the first dose. Beginning the next day, a dose is given twice daily, approximately 12 hours apart, for two consecutive days. Due to insufficient data, the manufacturer of AL recommends it not be administered to infants weighing less than 5kg or younger than two months. Namibia's National Malaria Case Management Guidelines, authored by the MoHSS, sets a more conservative minimum age of 6 months for AL, in addition to the minimum weight of 5kg. First trimester pregnancy is a contraindication, based on animal studies suggesting that foetal absorption could lead to early pregnancy loss. The additional contraindications to AL in the MoHSS national malaria policy, include complicated/severe malaria, prior allergic reaction to AL, and conditions that predispose the patient to prolongation of the cardiac QT interval. The latter include a personal history of cardiac dysrhythmia, a family history of prolonged QT syndrome, or concurrent medications that are known to prolong the QT interval. Cardiac QT prolongation is a known class effect of numerous antimalarial drugs. Notably, in a recent review of nine different clinical trials using AL-based regimens, no serious adverse events (e.g., syncope or sudden cardiac death) were found to be associated with AL administration.

AL is active against early gametocytes, therefore the drug has some transmission blocking effect. The addition of single dose primaquine (PQ), which is effective against gametocytes of all stages, has the potential to block transmission. For uncomplicated *Pf* malaria cases, the latest National Malaria Case Management Guidelines for Namibia indicate a new policy to give single dose PQ the first day of treatment, in addition to AL. Single dose PQ will be provided to all *Pf* index cases in the study once the new policy has

been implemented by the MoHSS. Additionally, it will be provided to household members and neighbours of index cases who are tested with an RDT and found to have uncomplicated *Pf* malaria infection. This will be all positive RDTs in the RACD arm, and anyone who is excluded from TPE, receives an RDT instead, and tests positive. Those receiving TP will not receive PQ.

Dihydroartemisinin-piperaquine (DP) is another safe and effective ACT regimen recommended by the World Health Organization (WHO), and is recommended as a second line therapy for uncomplicated malaria in many countries.[10,17–21] The drug is also considered to be an ideal drug for presumptive treatment due to the long prophylactic effect on new infections that may last for up to 63 days (PCR-unadjusted treatment failure: RR 0.71, 95% CI 0.65 to 0.78, two trials, 3200 participants, high quality evidence). In addition, dosing is once daily instead of twice daily as with AL.[11]The decision about using DP vs AL was discussed extensively with partners in this study and it was felt that DP was not an option because the drug is not registered in Namibia. Additionally, partners expressed concern about using a drug with a longer half-life, and the potential for drug resistance, given some recent reports from Southeast Asia of decreased efficacy of DP.[22]

It has been proposed that presumptive treatment should be administered by directly observed therapy (DOT), because high coverage is critical to success. People who are not ill may be less adherent to medication; however, adherence may be higher when the perceived risk of infection is high, as would be the case in this study, where a family member or neighbour will have been diagnosed with malaria recently. In a review of the 12 successful trials that utilized mass drug administration, six employed DOT or modified DOT. Drug distribution and observation was performed by community volunteers, local health workers, study authors and/or external organizations.[23]While strict DOT would ensure the highest adherence, it may not be practical for under-resourced malaria programmes, particularly during high transmission season when malaria staff are busy. Many people may be away at school or work during the day, making strict DOT challenging. In this study, we will utilize modified DOT, where the first dose is directly observed and reminders for subsequent doses will be provided by family and community members, and the study staff when they are conducting follow-up visits to improve coverage. Adherence will be assessed by pill count in people treated in the RACD arm and a sub-set of people treated in the TPE arm.

1.6 Reactive Vector Control (RAVC)

Namibia's malaria control strategy principally relies on vector control using indoor residual spraying (IRS). The MoHSS conduct IRS between October and December each year using dichlorodiphenyltrichloroethane (DDT) on traditional structures and deltamethrin (a pyrethroid) on modern structures with cement-plastered surfaces. As is common in areas with lower rainfall, the main vector in Namibia is *Anopheles arabiensis*. Standard, annual WHO susceptibility testing at a number of sentinel sites indicates that the vector remains highly susceptible to DDT and deltamethrin. A first limitation is that the single annual round of IRS, as currently practised, misses many houses because structures may be locked, households may refuse, or the spray round may not reach all communities. Second, although high quality application of insecticide is intended, it is difficult to guarantee consistent spray quality. Finally, to delay or prevent insecticide resistance it would be necessary to rotate insecticides of either the organophosphate or carbamate class, because these have a different mode of action than pyrethroids and DDT.[24]

For TPE to be most successful it is necessary to kill parasites in human hosts as well as the vector population of the target area. This will be achieved only if TPE includes a reactive vector control (RAVC) component. The malaria control programmes in many low transmission countries target IRS where they perceive malaria risk to be highest. Such targeting is driven, in part, by pragmatic factors related to insecticide cost, yet it also facilitates supervision and quality control. To be most effective, IRS targeting will be directed at foci with active transmission.

Long lasting micro-encapsulated pirimiphos-methyl (Actellic® 300 CS; Syngenta, Basel, Switzerland) has been shown to be highly effective as a residual insecticide against *A. arabiensis,* killing high proportions of mosquitoes for up to 12 months.[25] Reactive and focal spraying with Actellic 300 CS can provide high quality vector control in places where ongoing transmission exists or is likely. The long-lasting residual effect will

ensure that inward migrating mosquitoes are unlikely to survive. The targeted nature of RAVC will facilitate a high degree of quality, which may help compensate for possible shortcomings in the annual IRS campaign. As an insecticide of the organophosphate class, Actellic will not contribute to the selection pressure for resistance that is exerted by the current use of DDT and pyrethroids in Namibia.[25]

2. Rationale

2.1 Overall rationale

RACD may identify asymptomatic infections and hotspots, but there are logistical challenges such as specimen collection, laboratory testing, and the need to return to treat people who were negative by RDT but positive by molecular testing, which can lead to loss of follow-up. Molecular detection methods that are more sensitive than RDT or microscopy are costly, require significant laboratory expertise, and may still miss very low parasite density infections. Additionally, using molecular tests for diagnosis has not been sanctioned by the WHO, and therefore national programmes might be hesitant to use them. By eliminating the need to test people prior to treatment, TPE may be more feasible to implement and more effective.

For TPE to be effective it is necessary to kill parasites in the human and vector populations in the target area. However, one challenge of targeted pre-transmission season IRS is that it is difficult to predict where future infections will occur. A reactive approach, in conjunction with the pre-transmission approach, will ensure IRS coverage in the highest risk areas. Further, if there is unknown resistance to the insecticide used during pre-transmission season, the subsequent reactive use of a different, and presumably effective insecticide, will provide better protection.

2.2 Rationale for the study design and selected study outcomes

In this study, we will utilise a cluster randomized controlled study with 2x2 factorial design to evaluate 1) TPE in response to a passively identified index case compared to RACD, and 2) RAVC in response to a passively identified index case compared to no RAVC. The advantage of a cluster randomized controlled study design is that we are able to assess the impact of a community level/public health intervention while controlling for potential confounders that may independently lead to changes in health outcomes. The factorial study design is advantageous because it enables evaluation of two interventions independently, as well as the evaluation of the combined intervention. Assuming there is no interaction between the two interventions (as is hypothesized between TPE and RAVC), the 2x2 factorial study design allows for a smaller sample size (than would normally be used for a three-arm study) can be used to compare intervention 1 (TPE) with control (RACD) and intervention 2 (RAVC) with control (no RAVC). Specifically, it would require a comparison of 28 EAs, or clusters, in each arm to compare TPE to RACD, and to compare RAVC to no RAVC. A three-arm study would require 78 EAs, but the factorial design allows enables a similar analysis with just 56 EAs. Additionally, because the hypothesized effect is greatest in the “combination” cell, we can likely assess an effect using only the 14 TPE with RAVC EAs versus 14 RACD only EAs.

Effectiveness to interrupt transmission is the primary outcome of interest for this study. Entomologic inoculation rate (EIR) is the gold standard measure of transmission; however, given the low sporozoite rates among mosquitoes in low transmission settings such as Namibia, it is an impractical measure for this study. Instead, our primary outcome will be the cumulative incidence of confirmed, passively detected malaria cases in study EAs, in each arm, over two transmission seasons. Significant time and effort has been spent working with the MoHSS during the first phase of the trial to ensure that the passive surveillance system is as complete and as close to real-time as possible. While incidence is a standard measure captured through health facility reports, it does not capture asymptomatic infections in the community. Therefore, we will conduct cross sectional surveys before and toward the end of the study, at the end of the transmission season, to measure seroprevalence and infection prevalence. These additional measures of transmission were not selected as primary outcome measures because seroprevalence is an investigational diagnostic

method and prevalence of asexual and sexual stages may be too low for comparison with logistically feasible sample sizes.

An experience from China, targeting household members and neighbours of index cases, suggests that 80-95% coverage with TPE is needed to interrupt transmission.[8]There is no evidence to show that high coverage of TPE is feasible. Some challenges for high coverage include people's willingness to take medication without knowing their infection status and the time it takes for staff to explain the rationale for taking medication. As high coverage is critical for effectiveness, but is mainly an implementation challenge, a secondary goal of this study will be to determine the feasibility of achieving at least 80% coverage of each of the interventions among targeted, eligible people in target areas in each study arm.

We will evaluate other aspects of feasibility including safety, acceptability, costs, and adherence. We will collect serious adverse event data in all arms and compare counts of serious adverse events (SAEs). Acceptability of TPE vs. RACD, and RAVC vs. no RAVC, will be evaluated through participation rate, focus group discussions, interviews with participants and key stakeholders. The costs and relative cost-effectiveness of TPE vs. RACD will be evaluated by a costing exercise. In order to evaluate a strategy that can be feasibly implemented by malaria programmes, medication will be delivered using a modified DOT strategy. Ingestion of the first dose of the medication will be directly observed during the first visit to the community, and then the subsequent doses will be left with the participant to self-administer. Drug adherence will be measured by performing a pill count after selected interventions in the RACD and TPE arms.

3. Study Aims

The **overall objective** of this project is to conduct a critical evaluation of TPE vs. RACD and RAVC vs. no RAVC as a surveillance and response strategy for malaria elimination.

The **primary aim** is to compare the impact of TPE versus RACD, and RAVC vs no RAVC on incidence of confirmed, passively identified malaria cases. Our hypothesis is that TPE will result in a 50% lower cumulative incidence compared to RACD and that RAVC will result in a 50% lower cumulative incidence compared to standard spraying. In addition, the following **secondary aims** will be addressed:

Secondary aims

Effectiveness:

1) To compare the impact of each intervention package (TPE+/- RAVC, RACD +/-RAVC) on the following outcomes. Our hypothesis that TPE+RAVC will have the largest impact, followed by TPE - RAVC, followed by RACD + RAVC, and finally RACD - RAVC, on these outcomes:
    a) Incidence, passively detected at health facilities
    b) Prevalence of infection, among all ages, as measured by LAMP
    c) Seroprevalence, among all ages, measured by ELISA

Feasibility:

1) To compare coverage of each intervention package and determine the feasibility of reaching 80% coverage. Our hypothesis is that the 80% coverage is attainable for each intervention arm and for RACD, TPE, and RAVC individually.
2) To compare safety of the interventions individually and as packages. Our hypothesis that the risk of serious adverse events will not be higher in any one of the arms versus the other arms.
3) To compare acceptability of the interventions, individually and as packages. We will assess this via refusal rates and qualitative assessment. We hypothesize all study intervention will be similarly acceptable.
4) To compare the costs and cost-effectiveness of the intervention packages. We hypothesize that the costs per intervention event will not be higher for people receiving TPE compared to RACD, and may be cost-saving. We also hypothesize that the combination of TPE+RAVC will be most cost effective.

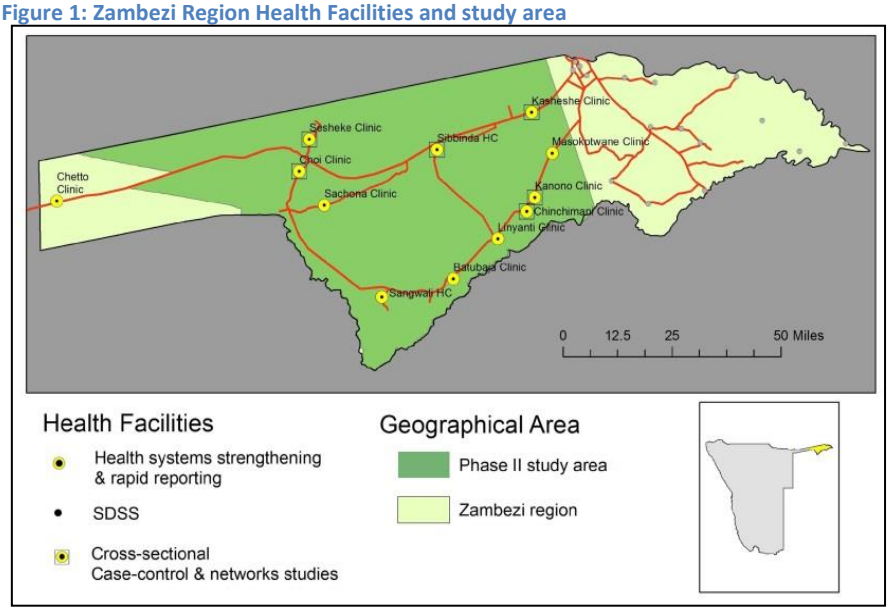
5) To measure medication adherence in both TPE and RACD. We hypothesize that adherence will be at least 80% in both the TPE and RACD arms.

4. Study Site

For Namibia to reach elimination by 2020 it is essential to address malaria where it will be the most difficult to eliminate, which includes Zambezi region due to higher incidence, tropical climate, and remote location. Zambezi region faces the additional challenge of imported malaria, due to its heavily travelled borders with Angola, Zambia, and Botswana, which people cross without the need for official documentation.

In 2015, Zambezi region reported 12,045 malaria cases, and was among the most malarious regions in the country. Zambezi region has a population of approximately 98,000; therefore, the region had approximately 123 malaria cases per 1,000 residents in 2015. The study area (See Figure 1) is comprised of the area of Zambezi region west of the capital, Katima Mulilo. This part of the region was chosen as it has significantly more cases than the eastern part of the region each year. The study area is specifically comprised of the EAs that make up the catchment areas of 11 health facilities: Batubaja Clinic, Chinchimani Clinic, Choi Clinic, Kasheshe Clinic, Kanono Clinic, Linyanti Clinic, Masokotwane Clinic, Sachona Clinic, Sangwali Health Centre, Sesheke Clinic, and Sibbinda Health Centre. The approximate population of the study area, according to the 2011 census is 35,381.

Figure 1: Zambezi Region Health Facilities and study area



Currently, two MoHSS staff focus on malaria in Zambezi region, a Surveillance Officer, and a Malaria Clinical Mentor. The Clinical Mentor works with health facility staff to ensure they are trained appropriately and follow MoHSS case management guidelines. The Surveillance Officer sits at Katima Mulilo Hospital with the MoHSS and supports the region's 2929 health facilities in surveillance and malaria case investigation. The MoHSS in Katima Mulilo employs Environmental Health staff who coordinate IRS campaigns each year, aiming for universal coverage, among other duties.

During Phase I of the study, beginning in 2014, the project provided support to help ensure the surveillance system was robust and captured all passively detected cases. Results have included nurses receiving higher marks on malaria diagnosis, treatment, and surveillance in training pre- and post-tests, a greater proportion of health facilities reporting their malaria statistics each week, all health facilities in the study area now have posters of the malaria treatment algorithm and the differential diagnosis for treatment strategy to help with diagnosis of non-malarial fevers. In mid-2015, a rapid reporting system was piloted by the project, whereby cases moved to being reported by tablet over the 3G network, usually within 24 hours.

During Phase II of the study this surveillance system will capture confirmed cases identified passively at all study health facilities, and those cases will trigger an intervention by the study team in selected EAs. If a person presents at Katima hospital or one of the five private health facilities resides in the study area, these index cases will also be included in the study.

Additionally, if feasible, RDTs and/or DBS will be collected from passively detected cases at health facilities in other areas of Namibia to better characterize genotypes of locally circulating parasites and more accurately characterize samples within the Zambezi region as locally transmitted versus imported. Additionally, cases and age-matched controls from an already existing study will be used to allow validation of antibody response to a set of *Pf* antigens that our group has identified as predictors of recent infection, unlike current available markers.[26] Therefore, once validated, these new markers will be used to measure seroresponse in the endline cross sectional survey (Appendices K and L).

5. Study design

5.1 Overview

We will evaluate the impact and feasibility of four intervention strategies (TPE with RAVC, TPE only, RACD with RAVC and RACD only) as surveillance and response strategies in the communities around passively detected, confirmed index cases using a cluster-randomised trial with a 2x2 factorial study design. Randomisation will occur at the administrative level of the EA. EAs will be pre-assigned to one of four intervention arms (see Figure 2).

Figure 2 – 2x2 Factorial Design

		TPE vs RACD arms	
		RACD (26 clusters):	**TPE (26 clusters):**
RAVC vs no RAVC arms	**No RAVC (26 clusters):**	RACD only (14)	TPE only (14)
	RAVC (26 clusters):	RACD + RAVC (14)	TPE + RAVC (14)

The assignment of these arms occurred in late 2015, and those assignments were used throughout the 2016 season. However, after assessing the 2016 data it was observed that one arm had only 1/3 as many cases as any of the other three arms. Therefore, the arms were re-randomised, re-assigning interventions to the previously selected EAs (see 6.1 Randomisation for more details).

With each new passively detected, confirmed index case reported from study health facilities, the intervention will be implemented in a Target Area of the EA. A Target Area includes the index case household and the surrounding households within 500m. At least 25 people will be enrolled in the study during each intervention, beginning with the index case household and then enrolling households in order of proximity to the index case. If fewer than 25 consenting people live within 500m of the index case, all eligible people will be asked to participate. Houses more than 500 m from the index case will never be enrolled in the study. Teams will visit each Target Area twice, enrolling as many eligible people as possible on each visit.

When considering resident eligibility and enrollment in the trial, the inclusion and exclusion criteria listed in Table 2 will be used:

Table 2. Inclusion and exclusion criteria for interventions

	Inclusion criteria	**Exclusion criteria**
Index case (as trigger for RACD or TPE)	• Malaria infection (local, imported, or undetermined origin) confirmed at study health facility	• Malaria infection identified through active case detection

	● Resides or overnight visitor to a study EA	
RACD or TPE intervention	● Index case resides or has spent the night in study EA in past 4 weeks ● Provides informed consent ● All non-index cases that reside or spent at least one night within 500m of the index case in the past 4 weeks	● Index case does not reside in study EA ● Refusal to participate ● Household received the intervention within the previous five weeks ● Treatment Exclusion: (but not inclusion in the study): Based on assessment by the study nurse, participants with complicated malaria or requiring further evaluation will be referred to a health facility ● Houses more than 500 m from the index case household will never be enrolled in the study
AL Administration	● Consent to take medication	● Pregnancy in the first trimester ● Previous regular menstruation with no menstruation for most recent four weeks ● Refusal of pregnancy test for females with history of menstruation but who have not menstruated in the past 4 weeks ● Weight < 5 kg ● Age < 6 months ● Severe malaria ● Known AL allergy ● History of cardiac dysrhythmia ● Family history of long QT syndrome ● Regular intake of QT-prolonging medication(s)
Pill count	● People who receive any number of RACD/TPE drug doses ● Provides informed consent	● People who did not receive RACD/TPE drug doses ● Refusal to participate
Reactive Vector Control	● Index case resides in study EA ● Head of household or responsible person in charge of household provides informed consent ● Index household and six closest households consent	● Household head refusal to participate (note that refusal to participate in RACD or TPE is not an exclusion criteria for RAVC) ● Received RAVC in the current transmission season ● Household is > 500 m from the index case ● Household sprayed by MoHSS within past 24 hours
Endline survey (early/ mid 2017)	● Reside or spent at least one night in the EA in the past 4 weeks	● Refusal to participate (Note: lack of participation in TPE or RACD is not an exclusion criterion)

5.2 Outcome measures

Table 3. Outcome measures

Outcomes	Indicator
Primary Aim	
Incidence	The incidence per person year of all RDT or microscopy confirmed local malaria cases identified by passive surveillance in study EAs after the first reported case during the study period. Does not include additional cases found through RACD.
Secondary aims	
Effectiveness	
Exposure	Seroprevalence to markers of recent exposure using ELISA (endline survey in mid 2017) in study EAs.
Infection prevalence	Prevalence of infection by LAMP in study EAs (endline survey in mid 2017).
Feasibility	
Coverage	Proportion of residents and present visitors who complete initial individual procedures for the study (finger prick for RDT in RACD arm, initial dose of AL in TPE

	arm, receipt of additional IRS in RAVC arm).
Adherence	Proportion of people who complete the course of medication among a subset of people initiated on treatment in TPE and RACD arms that are randomly selected to receive modified DOT, as assessed by pill count.
Prevalence of SAEs	Number of participants experiencing SAEs deemed possibly, probably, or definitely related to study medication or additional IRS, out of the total number of participants who received that intervention (TPE, RACD, RAVC, the packages of interventions).
Acceptability	Quantitative assessment (proportion agreeing to participate in RACD, TPE, and/or RAVC; proportion reporting that they would participate in future interventions at endline cross sectional survey) and qualitative assessment.
Cost	Cost per index case-level intervention.

6. Study procedures

6.1 Randomisation

Before year one of the study (February 2016 - December 2016), the study EAs were randomized as described below. However, there was an unexpected and significant outbreak of malaria cases during 2016 and after the completion of the first year of the study it was determined that incidence and case investigations in the study arms were significantly unbalanced, and therefore the study arms have been re-randomised. The description of both randomization processes are described below.

Year 1 Randomisation

The study area includes 102 Enumeration Areas (EAs). Study EAs were eligible to be included in the study if they had enough geographic data to assign cases to EAs and had at least one incident case of malaria in the previous three seasons. These criteria excluded 29 areas with missing information and 19 with no incident cases, leaving 54 EAs. To have equal numbers of EAs in each study arm, the list included 56 EAs. EAs were stratified by incidence in the previous transmission seasons and population size and randomly assigned to one of the four study arms (Figure 2). The trends in total incident cases from the study EAs are shown in Table 4. Although the data for 2014 are only available through May, as the retrospective data collection occurred May – August 2014, this timeline corresponds with the end of the transmission season and cases between May and December were not anticipated to have much impact on calculations of incidence. In addition, geographical reconnaissance was conducted to collect additional data about villages and health facility catchment areas. Depending on the results of those surveys, the final list of eligible EAs may change. If there are substantial changes the final randomization scheme will be updated. Any changes will be submitted for institutional review prior to implementation. The final randomization included 56 EAS, allowing for 14 in each of the four study arms.

Year 2 Randomisation

For the second year, the same 56 EAS will be re-randomized using a restricted rather than a stratified randomization. To guard against unbalanced incidence, we will add additional factors to the restriction process. The restriction will include the following criteria: equal distribution of EAs with 1 or fewer incident malaria cases in any of the 2013, 2014, or 2016 transmission seasons, balance in population size, population density, mean distance between households, mean distance to a health facility and incidence in the three years with EA level data. Although overall numbers of cases are available for 2015, cases for this transmission season were not assigned to EAs. Thus, only the 2013, 2014 and 2016 seasons will be used to balance incidence across study arms. A random set of 100,000 assignments will be generated and those meeting the restriction criteria will be selected. The final randomization allocation will be chosen from those randomly generated assignments which meet the restriction criteria.

Table 4. Incident, passively detected, confirmed malaria cases in study area (Jan 2012 – May 2016)

Year	2012	2013	2014*	2015	2016

					(Jan – May 15)
# Cases	91	429	667	251	1,477
# cases in study EAS from recent data	196	361	452	?	603

*Data only available for January through May.

Year 2 Randomisation

During the analysis of the first year of data from the randomized controlled trial, it was noted that the number of incident cases in each arm was significantly unbalanced. While the number of cases in three arms were relatively balance, with 182 in the TPE only arm, 196 in the RACD only arm, and 164 in the RACD + RAVC arm, there were only 60 cases in the TPE + RAVC arm. To address this imbalance, the Steering Committee agreed to re-randomize the study arms. The same EAs will remain part of the study, but the study interventions will be re-randomized amongst them using a restricted randomization process, with restrictions based on population density, distance from a health facility, and incidence.

6.2 Target Areas

A Target Area is defined as the index case households and as many of the closest households needed to be included to enrol at least 25 people. The houses will be approached in order of their proximity to the index case household. Houses more than 500 m from the index case household will never be enrolled in the study. This Target Area size was selected based on the RACD data from Engela, Namibia, and Swaziland where the mean number of people screened per index case was 24 to 32.

If a subsequent index case is reported in a Target Area that has already received an intervention, the RACD intervention will not be repeated at households that have received the intervention within the past five weeks. For the TPE arm, the intervention will not be repeated within five weeks or more than twice within 12 months. For cases identified during fieldwork, these will be reported through the MoHSS reporting system, but will not trigger a new intervention cycle.

Based on past surveillance data, and the fact that not all index cases will receive an intervention (subsequent cases within 8 weeks in households that already received an intervention be excluded), we estimate about 235 index cases per study year in our study EAs.

6.3 Community sensitisation and understanding

Prior to each season of the study, we plan to build awareness, secure commitment, and encourage participation from stakeholders at the national, regional, and local levels. We will meet with members of the MoHSS in Windhoek and Zambezi region and other stakeholders in the health sector and government. Once the appropriate officials have granted approval, we will sensitise health facility staff and community health workers, including meeting them at health facilities and distributing information sheets (Appendix A).We will work with community health workers and surveillance teams to sensitize community members in areas selected for TPE and RACD to discuss the study.

Each intervention EA will be randomly assigned an intervention before the study begins. Sensitisation in all EAs will occur before the study begins according to the intervention assigned. The index case will be contacted by telephone before the visit, if possible, and asked to notify other members of their household and their neighbours. Before the 2016/2017 malaria season the study EAs will be re-randomized, with the EAs included in the study remaining the same, but shifting which EAs receive which intervention to balance study arms. Sensitization about the change in interventions and re-randomizations will be included in the pre-malaria season sensitization in late 2016.

6.4 Index case capture and identification

Index cases will be identified at health facilities within the study area; cases that are confirmed by RDT or microscopy will be eligible for inclusion in the study. Per standard surveillance guidelines, the health worker completes the Case Investigation Form (Appendix C) and reports the case through the rapid reporting system within 24 hours. Index cases will then be invited to participate in the study by the nurse, letting them know that not all those invited to participate will be enrolled, since only those who live within a study EA will be included. For index cases who agree to be enrolled in the study, study procedures that are not already part of standard surveillance include a second finger prick at initial presentation to collect a dried blood spot (DBS) for malaria testing and storage of their sample for further malaria related research only. Any index case who declines to participate in the study will not be enrolled and their RDT will not be saved. For these cases, the MoHSS will then decide whether to investigate the case according to standard procedures.

After a case is reported through the rapid reporting system, the NVDCP Surveillance Officer and the study team may access those data via a secured, cloud-based database. If the case lives in a study EA, and has provided consent to participate in the study, a Field Investigator will call the index case, and if possible, schedule a visit to the home of the index case. During the household visit, the field investigator will double-check the household ID, capture GPS coordinates, and assign a household ID if there is not one. If a DBS was not collected at the health facility, if the index case consents (Appendix Q), the nurse will collect a DBS. If the implementation of a study intervention is outstanding (e.g. delayed reporting, index case unable to be reached), eligibility for enrollment will expire four weeks after the case was diagnosed at a study health facility.

6.5 Enrollment of a Target Area for TPE or RACD

When an index case meets the criteria to trigger an intervention, the Target Area around that case will be enrolled in the study (see Table 2). If a new index case presents within 5 weeks of when TPE or RACD was conducted for a previous index case, only households that did not previously receive an intervention will be included.

The study staff will begin recruiting participants from the home of the index case, and then move on to neighbouring households in order of proximity to the index case household. The team will attempt to enroll at least 25 people per index case, enrolling as many people living within 500m of the index case as possible during two visits. At a minimum, the team should continue until the 25th person is enrolled, then continue to enroll all remaining consenting members of that household. If the team has time, they should continue to enroll more people rather than stopping at the household with the 25th person. If less than 25 people live within a 500m radius the team will stop once all eligible, consenting residents have been enrolled.

On the first visit, the team will record the GPS coordinates of the index case household and will determine the closest households while in the field. If possible, this will be performed in advance using the household ID number assigned to the household during geographical reconnaissance, which is associated with a GPS location. The team will attempt to collect a GPS point of all the houses that are eligible to participate in the study, both those who participate and those who do not, with the permission of household heads (see Appendix D).

Follow-up visit protocol

- The team always visits every Target Area twice, enrolling at least 25 people, or all consenting people living within 500m, unless 100% of residents within the Target Area are enrolled on Day 1.
- The household where the 25th person lives must have all members enrolled, rather than stopping at the 25th person.
- Teams should not stop at 25 people unless they run out of time, but should continue enrolling participants until the second day is over.
- On the second visit teams must re-visit every household where 100% of residents were not given the opportunity to participate in the study, then move on to households that were not previously approached, in order of distance from the index case, within 500m.

The goal will be to complete two visits within 14 days of the index case identification date; however, visits can be initiated up to four weeks from when the index case was diagnosed. RACD or TPE interventions not initiated within four weeks, and not completed within eight weeks, will be closed.

6.5.1 Enrolling members of vulnerable groups

Vulnerable groups invited to participate in this study include females and children. Their participation in this study is critical because they represent high-risk groups for malaria infection.

Females – Pregnancy testing

In accordance with Namibian MoHSS national malaria policy, the artemether-lumefantrine intervention will be withheld from those females who are pregnant and may be in their first trimester. Pregnancy testing and consent are embedded in the individual questionnaire (Appendix F. Individual Level Questionnaire). Each female 10 years of age or older is asked whether she is pregnant, and if affirmative then by how many weeks.

(i) A female who acknowledges pregnancy within the first trimester (defined as under 14 weeks gestation) will be excluded from AL. If she is in the TPE intervention, she will then be offered an RDT. If she is in the RACD intervention, she will already have undergone RDT testing. In either case If the RDT is positive, she will be referred to the nearest HF for appropriate treatment.

(ii) A female who acknowledges pregnancy beyond the first trimester (defined as 14 weeks gestation of later) will be allowed to receive AL.

A females who indicates she is not pregnant, or does not know her pregnancy status, or acknowledges pregnancy but is unclear of trimester status, is asked whether she has ever menstruated in the past. If she indicates 'yes', she is then asked whether she has menstruated in the most recent four weeks. If she indicates 'no', she is offered a pregnancy test with the following language "I would like to offer you a pregnancy test, it only takes a few minutes and I will only tell you the results, no one else in your household will know." If the pregnancy test is positive, she is excluded from receiving AL. This scenario may occur in either the RACD or TPE intervention:

(a) in the RACD intervention, a pregnancy-test positive female will already have undergone RDT testing. If her RDT teset was positive, she will then be referred to the nearest HF for treatment per MoHSS guidelines;

(b) in the TPE intervention, a pregnancy-test positive female will next be offered an RDT, and if RDT-positive she will similarly be referred to the nearest HF.

Pregnancy testing consent is asked verbally in order to keep pregnancy test results private. Due to privacy concerns and cultural/family pressure towards sexual health of young women, parental consent is not obtained for females under 18 years of age who are offered pregnancy testing. Consent to or refusal of pregnancy testing is recorded on encrypted study tablets, as is the pregnancy test result. Females who are offered a pregnancy test per study protocol and then refuse pregnancy testing, will be excluded from receiving AL and referred to the nearest HF.

Children

If children are enrolled as index cases or in the community, the consent of a parent or guardian will always be sought. In addition, participants who are 12-17 years old will be asked for their assent to participate.

- If a child is an index case and the parent/guardian is unavailable at the time of the positive RDT, no second finger prick to collect blood for a DBS will be conducted. The child will be treated at the time of the visit according to MoHSS protocol. Permission to enroll the child in the study will be requested during the community level visit.

- If the child is a resident of a target area and no parent or guardian is available to give consent, basic information about the household will be collected, including location, number of residents, and household head name. The team will then revisit that household to attempt to receive consent from an adult. No person under 18 years old will be given an RDT or treated without the consent of a parent or guardian.

6.6 Reactive Case Detection (RACD)

A study team, made up of a field investigator, a driver, and a nurse, will arrive at the household of the index case and ask for permission to conduct RACD, checking in with the village headman first if he is available. Starting in the home of the index case, informed consent will be requested (see Section 11.1). If consent is obtained, a short survey will be administered at the household and individual level (see Appendices E and F), blood will be collected by finger prick for RDT testing with a CareStart RDT (which tests for *Plasmodium falciparum* and other species of *Plasmodium*) and a DBS, consisting of four spots, will be collected.

Anyone who tests positive by RDT will be treated by a study nurse on site per national policy with AL or with AL+PQ once the new policy has been rolled out. Anyone testing positive that is symptomatic and warrants further evaluation will be treated on site and referred to a health facility. Those treated will be administered the first dose of AL via DOT, will be informed that someone may return to conduct a pill count at the end of their treatment course, and will be instructed to save the drug packaging (see Appendix J). Cases detected by RDT in the community during RACD will not become new index cases in the study; however, the case will be reported to the MoHSS via the rapid reporting system. Subjects meeting any exclusion criteria, including pregnancy in first trimester (full testing details under 6.5.1) or refusal to take a pregnancy test if indicated, will be referred to the nearest health facility for treatment.

6.7 Targeted parasite elimination (TPE)

A study team, made up of a field investigator, a driver, and a nurse, will arrive at the household of the newly reported index case and ask for permission to conduct TPE, checking in with the village headman first, if he is available. Starting in the home of the index case, the study team will ask for informed consent from all residents to be treated for malaria, without a malaria test. If consent is obtained, the team will proceed with the household and individual level questionnaires.

For TPE, we will use AL, which is currently the first line drug used for uncomplicated malaria in Namibia. AL requires two daily doses for three consecutive days, for a total of six doses (see Appendix I). The first dose is followed eight hours later by the second dose. For days two and three, a twice-daily (morning and evening, 12 hours apart) dosing schedule is adopted. The first antimalarial dose will be administered by DOT. Subsequent doses will be left with the participant or guardian, with instructions on how to self-administer. Study staff will revisit target areas up to once more to enroll more residents. Those treated will be informed that someone may return to conduct a pill count at the end of their treatment course and will be instructed to save the drug packaging (see Appendix H).

AL will be dosed per manufacturer guidelines. The six-dose AL regimen will consist of adult dosages for adult patients and AL will be dosed to children according to weight- and age-based guidelines (see Appendix I). Participating children under 18 years of age will be weighed at enrollment to determine the correct dosage. Participants will be encouraged to take AL with a meal in order to maximize absorption, per manufacturer instructions. For infants and children unable to take tablets, drugs will be crushed, mixed with 1-2 teaspoons of water or juice and administered as a suspension. As part of the informed consent process, participants will be given instructions on what to do in the event of an adverse reaction (see Safety Section). The shelf life of AL is 24 months. Expired drugs will not be used.

The administration of AL will follow the Namibian national policy, according to which this agent will not be given to participants with: pregnancy in the first trimester (full testing details under 6.5.1), weight less than 5kg, age less than 6under two months, known AL allergy, severe malaria, personal history of dysrhythmia,

concurrent usage of QT-prolonging medication(s), or family history of long QT syndrome. In consultation with the MoHSS, the principal investigators have compiled a comprehensive list of all QT-prolonging medications that are available in the Study Area (Appendix F). Subjects taking any of these medications will be excluded from the TPE intervention. All females over 10 years of age will be asked about menses. Those who have reached menarche but have not menstruated in the past four weeks will not be given AL. Subjects meeting any exclusion criteria, including pregnancy in first trimester (full testing details under 6.5.1) or refusal to take pregnancy test if indicated will be tested by RDT during the intervention visit. Individuals who cannot be given Al due to these exclusions, as well as any female 10 years of age or older who declines a pregnancy test if indicated, will be tested by RDT during the intervention visit. Such subjects who test positive by RDT will then be referred to the closest health facility for treatment with a drug that is safe for them according to national policy, e.g. oral quinine for uncomplicated malaria in the first trimester and among infants smaller than 5 kg. For TPE participants who undergo RDT testing by the study nurse for the indications above, the same finger prick will be used to generate dried blood spot using four drops of blood. At the time that blood is collected for RDT testing, the same finger prick will be used to generate a dried blood spot. Four spots of blood will be collected for each DBS. Participants testing positive by RDT will be treated by the study nurse or, if indicated due to symptoms or to AL contraindications, referred to the closest health facility for treatment.

6.9 Reactive vector control

Half of all study EAs will receive reactive vector control (RAVC) in addition to RACD or TPE. The spray team will spray seven households in each Target Area in an RAVC EA that are within 500m of the index case household. The RAVC team will ask permission to spray each eligible house. Study households are eligible to receive RAVC regardless of whether they agree to RACD or TPE. The team will spray each household with the WHO approved insecticide, micro-encapsulated pirimiphos-methyl (Actellic® 300 CS).

On the day of RAVC, the spray personnel will inform household residents of the purpose of spraying and will give the household time to prepare and vacate the house. The household members should remove all household items, including water, food, cooking utensils and toys from the house. When possible furniture should be moved outside, if this is not possible, it should be moved to the middle of the room to allow easy access for spraying walls and covered. All wall hangings should be removed. When water jars cannot be removed, they should be covered. Pets and domestic animals should be tethered away from the house. Occupants must leave houses before spraying and any rooms occupied by sick people who cannot be moved will not be sprayed. All walls and the ceilings of all sleeping structures used by the household will be sprayed according to NVDCP guidelines at an application rate of 40 ml/sq m with a Hudson X-pert sprayer (H D Hudson Manufacturing Company, Chicago, Ill, USA). Rooms will not be sprayed if people or animals are present, or if household items are not correctly removed or positioned. It is estimated that the RAVC procedure from start to finish will take approximately one hour per residence.

Household members will be asked to mop up any excess solution from the floors and wash the floors with water before they allow young children back into the house. They will be reminded not to wash, paint, or re-plaster sprayed walls at least until the end of the malaria transmission season.

A household that already received RAVC in the current malaria season will not be eligible to be sprayed again in that season. At least six months must pass between administrations of RAVC in the same structure. At least one week must pass between standard MoHSS IRS and RAVC.

Those Target Areas not randomized to RAVC will receive no additional IRS, but should have had the opportunity to have their household sprayed by the MoHSS during the regular, annual spray season.

6.10 Adherence

In order to evaluate medication adherence, study staff will return to perform a Pill Count for participants who were prescribed AL in the RACD arm and a sampling of people given AL in the TPE arm. There are limited data on the expected adherence to three-day regimen among asymptomatic people. Among

symptomatic people, the reported adherence ranges from 39% to 100%.[27]Due to the return visit by study staff and perceived risk among people residing near an index case, we hypothesize that adherence for a complete course of AL will be equal in both arms, and at least 80%. The pill count will occur in one Target Area in each study EA, and therefore adherence data will be collected in 56 intervention events.

6.11 Acceptability

Acceptability will be assessed using mixed methods to triangulate findings. The quantitative assessment will be based on the participation rate in RACD and TPE +/- RAVC. We will also assess acceptability in the endline cross-sectional survey by asking if residents would be willing to participate if offered the intervention again (see Appendix V). The qualitative portion will explore the acceptability of RACD compared to TPE among participants, refusers, and key stakeholders. A pre-intervention qualitative assessment of acceptability was included in Phase I of the study and involves focus group discussions (FGDs) to explore acceptability of TPE and strategies for working with communities to increase the likelihood of acceptance of the interventions. The qualitative data collection will continue for the duration of the study. The results of this acceptability study will be used to refine the study on an ongoing basis, as well as strategies for malaria elimination in Namibia and other malaria-eliminating settings.

We will use interviews and FGDs to understand participants' situational perspectives in regards to the study.[28]The importance of using qualitative methods as an adjunct to clinical trials has been documented.[29]Additionally, this approach has been validated, as previous studies have used participant and key stakeholder interviews successfully to capture important information regarding community acceptability of new treatment modalities.[30,31]

Focus Group Discussions

We will conduct FGDs in Target Areas from each arm of the study. The goal of the FGDs is to identify barriers to malaria elimination strategies and to identify solutions where possible. We will conduct FGDs with participants after a study intervention has occurred. FGDs will be segregated by gender, with one FGD with each gender in each selected Target Area. Community leaders will be excluded from FGDs, but can be interviewed as key stakeholders to avoid tension. We will conduct 3-5 FGDs of approximately 7-12 people in each arm of the trial, continuing beyond that number if saturation has not been reached.

FGDs will explore why community members chose to opt in or out of the intervention(s), possible barriers and facilitators to RACD, TPE, and RAVC, and positive and negative experiences with intervention implementation.

All focus group participants will provide verbal informed consent for participation and audio recording of the session. FGDs will be held at a convenient location in the area where the intervention took place.

Participant, Refuser, and Key Stakeholder Interviews

Participant Interviews

To appreciate the reasons why people accept or refuse to participate in RACD, TPE, or RAVC, we will conduct semi-structured individual interviews with residents of Target Areas who were invited to participate in the study, both those who chose to participate and those who did not. Through a mix of open and closed ended questions, we will explore how community members view the interventions and why. Interviews will take place in the village where the participant resides or at the local health facility. All interviews will be audio-recorded with verbal consent from the participant. We will use purposive sampling to identify members of the community who have participated in the clinical trial.

Refuser Questionnaire

A short questionnaire will be given to those who refuse testing, treatment, or spraying at the time of refusal (see Appendix F). The questionnaire will ask about past participation in malaria screening and reasons for refusing participation in this study. These surveys will last approximately 5-10 minutes and participation is voluntary.

Table 5. Acceptability Assessment – Study population, sample size, inclusion and exclusion criteria

Aim	Study population and sample size	Inclusion criteria for Acceptability Assessment	Exclusion criteria for the Acceptability Assessment
Key stakeholder interview	People who hold leadership positions in government or health within Zambezi region; at least 12 people total.	● Male and female ● In a leadership position in Zambezi region ● Provide informed consent	● Refusal to participate ● Not in a leadership position
Refuser interviews	Everyone refusing TPE, RACD, or RAVC. If an entire household refuses, household head will complete.	● Refuses to participate in TPE, RACD or RAVC ● Agrees to a short anonymous survey	● Refusal to complete refuser survey ● Age under 15 years
Focus group discussions with study participants	Anyone who was eligible to be enrolled in the study within that Target Area. 3 – 5 FGDs in each arm of the trial. 12 – 16 total FGDs, 84 – 160 people, half with women, and half with men.	● Male and female participants and refusers ● Residents of selected Target Area ● Provide informed consent	● Refusal to participate ● Key stakeholder or in other leadership position ● Age under 15 years
Quantitative assessment	Participants in the study intervention and 2017 cross sectional survey. Both participants and non-participants in interventions.	● Invited to participate in study intervention, participating in the endline cross-sectional survey	● Refusal to participate in cross-sectional survey

Key Stakeholder Interviews

During the trial, key stakeholders will interact with the community members to facilitate the trial. Local stakeholders, including members of local, district, and regional leadership and health facility and community health workers, will be engaged through key stakeholder interviews. These interviews will explore the role of the key stakeholder in the clinical trial, experience with malaria elimination in Namibia, acceptability of RACD, TPE, and RAVC as strategies in their communities, and reasons community members agree or disagree to receive testing and/or treatment.

Key stakeholder interviews will last approximately 45 minutes. We will interview at least 12 key stakeholders including two from each constituency involved in the study (Judea, Kongola, Linyanti, and Sibbinda) as well four people within regional government and health leadership. When considering eligibility and enrollment in the acceptability assessment, the inclusion and exclusion criteria listed in Table 5 will be used.

6.12 Costing study

The goal of the costing study is to compare cost per intervention event in TPE versus RACD +/- RAVC. Our hypothesis is that the costs of TPE per intervention event will be lower than RACD due to the cost and personnel timesavings from not performing a diagnostic test. Of note, if TPE is more effective, cost per index case may be higher in the TPE arm due to decreasing incidence; however, if TPE is more effective, the cost per case averted (compared to RACD) may be lower. We will collect detailed expenditure data on costs of delivery of TPE, RACD, and RAVC interventions. We will collect total costs (including costs for all consumables, as well as staff time) for RAVC to give the MoHSS an estimate of total cost and feasibility of implementation.

6.13 Drug Potency Study

A sample of the study drug will be pre-identified and transported on field visits throughout the trial. At the end of the trial, the sample will be tested for potency. This is designed to reconcile manufacturer instructions that warn against storage above 30°C because temperatures in the study area are regularly above this threshold.

6.14 Serology validation sub-study

The purpose of this sub-study is to validate putative markers of recent malaria exposure, which will be used in the endline survey (see Section 6.15). This sub-study will enroll approximately 300 individuals: 100 RDT-positive and LAMP or PCR-confirmed cases as well as 200 age- and gender-matched, RDT, LAMP, and PCR-negative controls). These cases and controls will be randomly selected from the Phase I case control study and Phase I cross-sectional survey study participants. Enrollment in the serology validation sub-study will consist of two additional visits and will begin approximately 6-12 months after cases and controls were initially identified by RDT in the corresponding Phase I study.

For the first serology sub-study visit, staff will contact the previous study participants by phone, and then visit them at their homes. After new consent is obtained, a short questionnaire regarding malaria risk factors will be administered, an RDT will be performed, a DBS containing four spots, and a 180 μL whole blood sample in a microtainer will be collected. Samples from each of the two sub-study visits will be labelled with a barcode encoding a unique alphanumeric serology sub-study identifier. Study staff will return for up to two additional visits per participant per time point to ensure high capture.

For the second and final serology sub-study visit, the above procedure will be replicated 6-12 months after the first sub-study visit. Informed consent will be collected at each sub-study visit.

Analysis of these samples will refine our current knowledge of serologic markers of recent (within 9 months) versus remote (greater than 24 months in the past) malaria exposure in low endemic settings. The antibody markers we identify as having the highest degree of association with the first and not with the second time point, will be used in the post-intervention endline survey to measure seroprevalence. More broadly, this serologic information will help inform future tools used in Namibia to measure exposure and to document interruption of transmission.

6.15 Endline Survey

A follow-up blood survey and questionnaire will be conducted toward the end of the study in early/mid 2017. A sample of residents, representative of the four study arms, will be requested to participate. After informed consent is obtained, a short household and individual questionnaire will be administered. A finger prick will be performed to collect blood for a CareStart RDT, to test a new highly sensitive RDT, and to collect a DBS as well as ~300 microliters of whole blood in a microtainer. Approximately 25 households will be enrolled in each of the 56 study EAs, for approximately 5,040 people. The 25 households will be randomly selected from among all households in that EA. Residents who did not participate in the intervention are eligible for participation as the goal of the study is to evaluate community level impact. Study staff will return for up to one additional visit to ensure high capture.

The main purpose of the endline survey is to perform measure prevalence of malaria infection. The endline survey will also collect blood samples to perform serological assessments looking at markers of recent exposure will enable comparisons of recent transmission between the two arms, and thus impact of RACD vs. TPE +/- RAVC. A serological assessment looking at markers of past exposure will enable comparisons of baseline exposure between the two arms. These samples will also be used to measure infection prevalence using quantitative PCR.

A secondary purpose of the endline survey is to measure the diagnostic accuracy of a new highly sensitive RDT (HS RDT) which can detect the presence of *Pf* and is predicted to be ten times more sensitive than current RDTs. The HS RDT will be run by nurses in the field in parallel to the Carestart RDT and the proportion of participants positive by HS RDT will be compared to the proportion positive by quantitative PCR and quantitative HRP II assay (HRP II is the HS RDT's analyse) to determine the sensitivity, specificity, positive predictive value and negative predictive value of the HS RDT.

7.0 Safety and Risks

The safety risks associated with participation in this trial are expected to be minimal. The study drug, AL, is well tolerated. Prior to AL administration, participants will be asked about known allergy, past adverse reactions felt to be associated with the medication, and other contraindications (see Table 2). Participants will be restricted from taking the medication if such a history is reported. Participants who test positive during our study but cannot safely receive AL will be referred to the nearest health facility to receive an alternate antimalarial medication per MoHSS policy.

For RDT positive cases found to have uncomplicated *Pf* infection, single dose PQ may be additionally administered if the MoHSS national policy endorsing this intervention is initiated during the time period of our study.[32] Pregnant women and infants under one year of age will be excluded from PQ.

Monitoring of serious adverse events (SAEs) potentially related to AL or Actellic CS will occur passively and actively (see Sections 7.2 and 7.3). Participants will be instructed to seek care at their local health facility or to call the on-call Study Nurse if they experience any adverse reactions while or after taking AL or after IRS with Actellic. When any adverse event is reported, a study nurse will complete an adverse event reporting form.

During the pill count, the study nurse will ask participants about possible toxicities, with any affirmative answer triggering the completion of an adverse event reporting form. All serious adverse events will be reviewed by the study nurse within 48 hours of notification, who will then discuss the event with the study physician (see Section 7.1). The study physician will assess causality by collecting additional data on the relationship between the drug and the event and will recommend whether the participant remain in or be withdrawn from the study, advising the study nurse and/or health facility worker accordingly. For each SAE, a separate SAE form will be completed (see Appendix N).

7.1 Passive identification of SAEs

Prior to the start of the trial, a training took place at each of the 11 study health facilities to educate health facility staff on adverse event reporting procedures and forms, and to share the phone number of the on-call Study Nurse. For adverse events detected at the health facilities, health facility workers have been trained to notify the Study Nurse immediately. The Study Nurse will be available 24 hours per day, seven days per week on a mobile phone reserved for this purpose. The Study Nurse will investigate each adverse event within 48 hours of notification, collecting pertinent information, classifying severity (see Appendix M), and filing the report. For all SAEs, the Study Nurse will discuss management with the Study Physician, who will advise whether the participant should continue or stop treatment due to safety concerns. Study personnel will assist with referrals to the local hospital, if indicated by the Study Physician. For less serious symptoms, the Study Nurse will advise health facility staff on management.

Participants will be given the telephone number of the on-call Study Nurse and may report adverse events directly. Management of such events will follow the same guidelines, with SAEs being mandatorily discussed between the Study Nurse and Study Physician, and with lesser severity AEs being managed by the Study Nurse directly (with added input from Study Physician at the discretion of Study Nurse).

For each adverse event, the Study Nurse will arrange a follow-up visit within 72 hours at a convenient location (at home, school, or if indicated a health care facility). If this is in response to a SAE, the visit will include the Study Physician. Subsequent follow-ups of the adverse event will continue until resolution is documented.

7.3 Active identification of SAEs

During the pill count (see Section 6.10), participants given AL in the RACD arm and to a randomly selected subset of participants in the TPE arm, study staff will ask participants about possible toxicities from the study medication. This inquiry (see Appendix H) will utilize an open-ended method to assess for side effects and

includes documentation of what immediate measures were taken by study staff members to alleviate an adverse reaction. Any affirmative answer will trigger the completion of an adverse event reporting form.

7.4 Expedited reporting of SAEs and SUSARs

The Study Physician will report each SAE and serious unexpected serious adverse reactions (SUSAR) to the management team immediately. After management and PI review, the information will be transmitted to the Data and Safety Monitoring Board (DSMB) within one week of occurrence and will be reported to the MoHSS Therapeutics Information and Pharmacovigilance Centre in parallel (Room 21, Basement Area of Windhoek Central Hospital, Tel 061 203 2312, Fax 061 22 66 31/ 088 618 776, info@tipc.com.na). Reports of SAEs that are classified as possibly, probably, or definitely related to study intervention, and reports of all SUSARs will be submitted to the IRBs at UCSF, UNAM, MoHSS, and LSHTM, within 7-10 days of occurrence, per corresponding IRB stipulation.

7.5 Management of participants with SAEs

If a study participant experiences an SAE classified as related to a study drug, decisions on whether the participant should complete treatment or stop will be made by the health facility worker providing treatment at the health center in consultation with the Study Physician. If the participant does not report to a health facility, this decision will be made by the Study Physician in consultation with the Study Nurse. Factors that will be considered will include the type and severity of the event and suspected strength of the association between drug and the event (possibly, probably, or definitely related). In all cases, the potential risks and benefits will be weighed and decisions will be guided by the best interest of the patient. The Study Physician will investigate to assess associations and severity, and will follow up with cases to ensure resolution. The Study Physician may consult with his or her physician colleagues to review associations and severity.

7.6 Adverse event monitoring - Data and Safety Monitoring Committee

A DSMB will be assembled, consisting of at least four members who are independent of the project and who have not contributed significantly to the project's design. Members will include experts in statistics, epidemiology, clinical trial design, and a clinician. The DSMB will elect a Chair and a Secretary. Depending on the agenda, independent advisors or experts can be invited to the meeting, upon approval by the chair and secretary. The DSMB, principal investigators, and sponsors will agree on the rules for reporting safety data during the course of the project, frequency of formal meetings (likely quarterly), and the rules for recommending premature termination of the project on grounds of safety or endpoint futility. The DSMB will review the study protocol and analytical plan prior to the onset of the study and will review SAE and SUSAR reports during the trial. After immediate management by the Study Physician, final decisions regarding continuation of study participation for participants experiencing SAEs causally related to AL will be made by members of the DSMB. See Appendix P for the DSMB Terms of Reference.

Meetings

The committee will meet at regular agreed-upon intervals, likely quarterly, and as needed if safety concerns necessitate. DSMB members are expected to attend meetings in-person or by teleconference, and should not rely upon substitute representatives. Members will participate in email discussions as necessary, and will be updated regularly on TPE progress and activities.

Stopping guidelines

The DSMB members will make decisions about discontinuation of the study. Stopping guidelines will be based on the prevalence of serious adverse events deemed to have a causal association with the study intervention as well as based on enrollment and consequent likelihood of endpoint assessability.

7.7 Potential risks and discomforts

Randomisation
In this cluster-randomized trial, participating EAs will be randomly assigned to one of four intervention arms (RACD +/- RAVC, or TPE +/- RAVC). One intervention may prove to be more or less efficacious, more or less well-tolerated, and/or more or less safe than the standard of care (RACD alone). Thus, there is the risk that EAs will be randomized to a less efficacious, less well-tolerated, and/or less safe study arm. However, such risks associated with randomization in this study are likely to be low.

Artemether-Lumefantrine
Artemether-lumefantrine has an excellent efficacy and safety profile and is the first-line treatment for uncomplicated malaria in 23 African countries, including in Namibia. Side effects that have been described in recipients of AL include headache, dizziness, loss of appetite, generalized weakness, fever, chills, fatigue, arthralgia, myalgia, nausea, vomiting, and abdominal pain. We will monitor for AEs and SAEs during this trial.

In general, ACTs, such as AL, are not recommended for use in the first trimester of pregnancy due to insufficient safety data regarding teratogenicity. To minimize any safety risks associated with AL treatment, we will not offer this agent to women in their first trimester or to postmenarchal, pre-menopausal women who have experienced no menses in the past four weeks. Due to limited data in infants under 5 kg, these participants will not be administered AL either. In accordance with Namibia's national malaria policy, infants under 6 months of age will not receive AL, nor will patients with severe/complicated malaria receive AL. Participants who have tested positive by RDT and who, based on the exclusions above, cannot be given AL safely, will be referred to the nearest health facility, where they can be evaluated to receive an alternate MoHSS-approved agent.

RAVC using Actellic CS
Actellic CS has an excellent human and environmental safety profile. The spray presents no significant risk to spray operators, household members, or the environment, when used correctly. It is possible that insecticide left unattended could be accidentally ingested by a child. To prevent such an event, spray operators will not leave insecticide unattended or unlocked in their vehicle. Study personnel who will directly be handling Actellic CS will attend MoHSS spray trainings in order to be educated on proper safety measures.

Blood draws
The potential risks of drawing blood from a finger-prick include temporary discomfort, pain, transient bleeding, bruising, skin infection, and fainting. The volumes of blood taken will be too small to produce any adverse physiologic effects from blood loss anemia and overall the aforementioned risks associated with blood draws are likely to be low. Study staff will be trained in the proper conduct of a finger-prick according to standard operating procedures to minimize the risk of discomfort and infection.

Positive malaria tests
In the RACD arm and the serology sub-study, RDT will be provided to each participant. Complimentary treatment will be offered if the RDT result is positive, provided the participant does not have signs of complicated/severe malaria and has no contraindications to AL. Participants with positive tests will be told to seek care at the health facility if their illness worsens. It is possible that for some cases in the community, the RDT will be negative, but the subsequent molecular (PCR or LAMP) test will be positive. This most commonly occurs when parasitaemia is below the level of detection for RDTs, but not below the level for LAMP or PCR. These participants will not be treated, as performance of LAMP or PCR is for research purposes. The risk of developing symptomatic or severe illness is very low from a presumably low parasitaemia in an RDT-negative asymptomatic individual. Of note, RDTs are used nationally at the point of care in health facilities, with treatment based on the result of the RDT and not on a confirmatory molecular test.

Confidentiality
The risks associated with loss of privacy in this study are likely to be low. To ensure confidentiality is maintained, all information will be treated as private by study personnel, and records kept securely in locked filing cabinets and offices. Electronic records will be kept on a secure, firewall- and password-protected

server. For all data collected as part of the study, participants will be assigned a unique identification number. No personal identification information such as names will be used in any reports arising out of this research. All project staff will be trained on procedures for maintaining confidentiality. Study staff will routinely discuss what other measures can be taken to minimize risk as issues arise during the study.

Compensation

Participants will not be paid to take part in this study. Most assessments will be conducted at households, which will eliminate the need for participant travel and minimize opportunity costs for the participants. Any diagnosis and treatment associated with the study will be provided free of charge.

8.0 Laboratory procedures

The laboratory procedures described below will be followed for all laboratory-based activities conducted during this project. The laboratories performing these tests include the UNAM campus in Windhoek and Katima Mulilo and UCSF. LAMP, PCR, and possibly ELISA, will be conducted by UNAM. Parasite genotyping, and possibly ELISA, will be performed at UCSF. Parasite species identification with PCR will be performed at either UNAM or UCSF.

8.1 Rapid diagnostic tests

Carestart RDTs will be used in the field to determine malaria infection status, and will be performed on participants every time a blood sample is collected. These RDTs can detect whether *Pf* infection is present or absent, and whether any *Plasmodia*, including *Pf*, is present or absent. RDTs will be performed according to the directions provided, using the blood transfer device and reagent provided by the manufacturer. Nurses associated with the project will perform tests and results will be available within 20 minutes. The results will be provided to the participant or their parent/guardian verbally and will be recorded. Symptomatic and asymptomatic participants who test positive for malaria will be treated on site by a study nurse.

During the cross-sectional endline survey only, we will test the diagnostic accuracy of a new highly sensitive RDT (HS RDT), which can detect whether *Pf* infection is present or not and is estimated to be ten times more sensitive than current RDTs. Study nurses will use a finger prick blood sample to run the Carestart and HS RDTs in parallel, according to the manufacturer's instructions. Results will be available within 20 minutes and will be recorded by study staff. Participants in the endline survey will be treated according to the results of the Carestart RDT since the HS RDT is in the prototype phase and is not licensed for use by the WHO.

8.2 Filter paper sample collection

Blood spots will be collected onto filter paper for future molecular studies for research purposes only. Filter paper (Whatman 3MM) will be pre-cut into individual squares and stapled to a thick card that will serve as its cover. Blood spots will be collected onto the filter paper in volumes of approximately 25 µl aliquots per blood spot (4 blood spots per card). Filter paper samples labelled with the individual's barcodes or ID number on the covering cardboard, and will be allowed to dry at ambient temperature and relative humidity before closing the card over the filter paper (like closing a matchbook). Filter paper samples will be transported from the field in a Ziploc bag then placed in a stock card filter paper box with desiccant and humidity indicator card and stored in a freezer in Zambezi region until they are transported to the lab at UNAM in Windhoek where they will be stored at -20°C.

8.3 Molecular Testing

Dried blood spots will be extracted using the Chelex method with Tween. Whole blood samples will first be centrifuged to remove and save plasma. Samples will first undergo LAMP testing using the LAMP PAN detection kit, followed by testing with the *Pf* detection kit if PAN positive. All RDT or LAMP positive samples and 10% of negative samples will undergo nested cytochrome B PCR testing with species specific identification using a restriction digest.[33] Other molecular studies may include quantitative PCR, as well as analyses of polymorphisms in parasite and/or human genes for mutations that may affect clinical malaria

and genotyping of malaria parasites. Molecular studies will be performed only for malaria research purposes and will have no impact on the clinical management of study participants.

8.4 Genotyping

Genotyping of *P. falciparum* will consist of a panel of microsatellites and/or single nucleotide polymorphisms (SNPs) located throughout the genome. Briefly, DNA samples will be amplified in a multiplex pre-amplification step followed by amplification of microsatellites in individual reactions using fluorescently labeled primers, and sized using denaturing capillary electrophoresis. Multilocus genotypes from mixed infections will be reconstructed, where possible, by quantifying alleles at each locus. Genotyping of additional loci, potentially including SNPs and/or targeted deep sequencing, will be performed as needed. Genotyping will be performed only for research purposes and will have no impact on the clinical management of study participants.

8.5 ELISA

Serology will be used to measure anti-malarial antibodies for the serology validation study and to measure impact of the trial interventions. Serology will also be used to measure levels of parasite HRP II antigen from whole blood as part of the endline survey for the HS RDT evaluation since the HS RDT detects HRP II in whole blood to determine *P. falciparum* infection status. Using dried blood spots and serum from whole blood, ELISA assays for antibodies will be performed using previously described methods.[6]Briefly, antibodies will be eluted from DBS and assayed to detect antibodies against the *Pf* blood stage antigens merozoite surface protein-1 (MSP-1_{42}) and apical membrane antigen-1 (AMA-1), both biomarkers of *Pf* exposure. Other antigens that are sensitive and specific for recent exposure that are undergoing evaluation will also be used. ELISA assays will be performed in duplicate and optical densities recorded. Other serologic platforms, including bead array and protein microarray, may be used to analyze responses to multiple antigens if available. ELISAs will be performed only for research purposes and will have no impact on the clinical management of study participants.

8.6 Sample storage for future studies

DBS, plasma, and extracted DNA will be maintained at -20°C. After the study period, blood samples will be stored for future malaria studies. Consent forms include a statement about future testing. Samples will be stored for 25 years, so that if there are new cases after elimination, past samples are available for genotyping purposes, as recommended by WHO.[34] Comparing new strains to past strains will help distinguish between imported and local infection. Re-emergence of new cases could occur more than 20 years after elimination as shown by North and South Korea, which eliminated malaria in the 1970s, but then experienced a re-emergence in the 1990s.

9.0 Entomological management

As vector numbers are expected to be low, this study will not include entomological outcome measures. However, since one of the interventions consists of vector control, it will be necessary to monitor (1) vector susceptibility to insecticides; (2) species composition; and (3) spray quality on walls.

9.1 WHO insecticide resistance testing

Susceptibility of the vector population to the four classes of insecticide will be performed at baseline and during the final year of the study in each of the four study arms. Adult *Anopheles*, reared from larvae and the F-1 progeny of wild females, will be tested using standard WHO susceptibility tests.[23] Mosquitoes will be exposed to impregnated filter paper discriminating dosages of deltamethrin (0.05%), DDT (4%), bendiocarb (0.1%) and Pirimiphos Methyl (0.25%). Percentage mortality and median time to knockdown will be measured. If insufficient mosquitoes are available, exposure to Pirimiphos Methyl will be prioritized, followed by exposures to DTT, deltamethrin, and bendiocarb (in that order).

If sufficient mosquitoes are found and if there is evidence of resistance, samples will be exposed to different concentrations of insecticide on filter paper and mortality will be assessed 24 hours post-exposure to obtain

LC50 data, or exposed to the standard WHO diagnostic dose for varying lengths of time to estimate LT50s. All specimens will be identified to species level.

9.2 Mosquito identification

Mosquitoes will be identified by microscopy and the numbers of identified species recorded. Funds permitting, *An. Gambiae* complex and the *An. Funestus* group will be identified by PCR. [24]

9.3 Spray Quality

WHO cone bioassays will be conducted on a sample of walls within one month of spraying, using insectary reared susceptible mosquitoes.

10.0 Data management

10.1 Quality assurance and quality control

All study personnel will be trained in the project objectives, methods of effective communication with study participants, collection of high quality data, and principles of ethical research practice. Study personnel will receive additional training specific to the tasks they will perform within the project, including interviewing techniques, administration of surveys, completing questionnaires, and use of tablet devices. Standard Operating Procedures (SOPs) will be written for all project activities and booklets of all relevant documents provided to each member of the project team. Weekly meetings will be held by the Site Manager to assess progress of the study, address any difficulties, and provide performance feedback to the members of the study group. Any corrections to data collection forms will be made by striking through the incorrect entry with a single line and entering the correct information adjacent to it, according to Good Clinical Practice guidelines. The correction will be initialed and dated by the study personnel member.

10.2 Records & storage

The study staff will maintain appropriate medical and research records for this study in compliance with the principles of Good Clinical Practice and regulatory and institutional requirements and in compliance of the requirements for the protection of confidentiality of participants. Only study personnel members will have access to these records. All forms with participant names will be kept in a locked cabinet or office when not in use, and the key kept by the Site Manager. All information coming from health facilities and data collected during field activities will contain patient/participant names. These names are crucial for follow-up. However, when data are shared outside of the Senior Management Team, participants will be identified only by their study ID number. All information will be stored in HIPAA compliant cloud-based databases, maintained by UCSF, UNAM, or the MoHSS. Once the study is complete, all data will be de-identified, with household and individual study identification codes remaining to link questionnaires to samples. Data will be stored for at least 5 years in secure databases. Authorized representatives of the sponsor, the ethics committees, or regulatory bodies may inspect all documents and records required to be maintained by the principal investigators. The principal investigators will allow all requested monitoring visits, audits, or reviews.

11.0 Statistical considerations

11.1 Overall study area sample

Based on 2011 census data and the estimated growth rate of the population, the overall population in the catchment areas of the 11 study health facilities is approximately 35,381 people. From January 2012 to May 2014, 19 of the 102 EAs had no recorded cases, and an additional 29 had insufficient geographic data to assign cases. In the selected available sample, EAs vary in population size from 100 to 583 persons, the arithmetic mean number of people per EA of 300. Because the population size of the EAs varied, we used the harmonic mean population size in the selected EAs (267 people per EA) in calculations of detectable differences. EAs will be randomized to one of four arms, with a minimum of 14 in each arm (56 total EAs). In

2016, there was an unexpected outbreak of malaria, and staffing was not sufficient to investigate all cases that presented with incident malaria. At the end of 2016, we determined that investigated cases were not balanced between study arms, and that protocol had not been followed as intended. We therefore decided to re-randomize the existing study EAs and re-launch the study. The revised restricted randomization approach is discussed in section XX above. EAs will be randomized to one of four arms, with 14 EAs in each arm (56 total EAs).

11.1.1 Sample size for the interventions

As defined above, a Target Area is defined as all people living in the six households closest to an index case detected via passive surveillance and who resides in a study EA. People who live up to 500m from the index case may be included if a minimum of 25 people have not been enrolled in the study within the first six households.

For the 2015-2016 malaria season, estimates on the samples size for the interventions were based on 2013 – 2014 annual incidence data. At the time, actual population was calculated at 16,200. To compensate for the uneven size of EAs, the harmonic mean of cluster size (267 per EA) was used to calculated the effective sample size of 13,884. Incidence was calculated at 19.5/1000 and assuming 50% decrease due to TPE, and 50% due to RAVC, we anticipated 117 index cases during the first year of the study, and enrollment of 2925 participants for the study intervention (25 per index case). Due to a delayed study launch and limited staffing, we enrolled 1501 participants in the first year of the study.

For the second year of the study (2016-2017), the expected sample size for the interventions has been updated based on measured incidence during the 2015-2016 malaria season and updated figures for the population (based on updated estimates from the geographical reconnaissance survey). The population has been re-estimated at 18,022 people residing in the study enumeration areas (EAs). Using the harmonic mean size of EAs (276 per EA), the effective sample size is 15,456. Using the same assumptions regarding the effectiveness of TPE and RAVC, we anticipate 206 index cases in the second year of the study. With 25 people/index case receiving the intervention, we expect 5150 encounters. Based on preliminary RACD data, we anticipate 10% of encounters will occur in people who previously received an intervention during the study period (repeated or overlapping Target Areas), resulting in 4,635 unique people. If 5% of people refuse an intervention, the total estimated number of people we will consent and screen for the second year of the study is 4403. Considering the number enrolled in year one (1501) the total enrollment for the 2 years of the study is expected to be 5904.

Table 6 Incidence and effective sample size estimates for year 2

	Pre-intervention	RACD no RAVC	RACD plus RAVC	TPE no RAVC	TPE plus RAVC	Total all study arms
Number of EAs	56	14	14	14	14	56
Incidence	33.45	25.09	12.54	12.54	3.14	13.33
Effective population (based on Hayes Moulton)	15456	3864	3864	3864	3864	15456
Incident cases per year	517	97	48	48	12	206
Potential participants encountered (25 per index case) for study year 2	--	2423	1212	1212	303	5150
Unique people expected to be enrolled for study	--	2181	1091	1091	273	4635

year 2						

*Estimated index cases and enrollment updated per 2015-2016 incidence for second year of study.

11.2 Power to detect differences in primary outcome –Incidence of new infections

Our primary study outcome is the incidence of passively detected, confirmed local malaria infections in the overall population of the EAs randomized to 1) TPE vs. RACD and 2) RAVC vs no RAVC. Incidence during the 2015-2016 transmission season in the study areas was 33.45 malaria cases per 1000 persons per year. To estimate power to detect differences in incidence we used a sample size of 56 EAs with an estimated harmonic mean of 276 people per EA (total effective sample size of 15,456) for the overall sample. This is a conservative estimate, using a sample size lower than the total population (estimated 18,022) to account for the effects of clustering in unequally sized clusters and 14 EAs per study arm. The coefficient of variation for incidence among the study EAs has been below 0.95 in each of the previous seasons and we used 0.95 as the estimated coefficient of variation. We hypothesize that introduction of RACD (which has not been consistently implemented in these areas) will decrease incidence to 25.09 per 1000 per year. As there is no available data to suggest that RACD using RDTs is an effective method to decrease transmission, it is possible that the incidence will not decline. However, this will not have a negative impact on our study, as it would only improve our power to detect a difference between the study intervention and control. Both trial interventions are hypothesized to reduce the incidence in the study population. We assumed an effect of 50% reduction (rate ratio 0.5) for both TPE compared to RACD and RAVC vs no RAVC. We further assumed a multiplicative effect of the two interventions combined, or a rate ratio of 0.25. Using these assumptions and the sample size as described above we would have 80% power to detect an effect of RAVC vs no RAVC and 80% power to detect an effect of TPE vs RACD and 80% power to detect the hypothesized difference between the combinations of TPE and RAVC vs RACD with no RAVC. We used the equations suggested by Hayes and Moulton to calculate the detectable differences with our sample size.[35]

11.3 Secondary outcome on effectiveness - Seroprevalence

In mid-2017, a cross sectional survey with a cluster sampled design will be used to measure seroprevalence. Within each EA, 25 households will be randomly sampled. With an estimated household size of 4.5 and 80% coverage of selected people, we expect to sample 6,300 individuals and enroll 5,040 across the 56 EAs. Based on preliminary data from another similar setting, we expect seroprevalence in the RACD arm to be approximately 10%.[6]

Accounting for the clustering of cases and assuming 10% seroprevalence in the RACD arm, with a sample size of 2,520 in the TPE arm and 2,520 in the RACD arm, the endline cross-sectional survey will have 80% power to detect a minimum detectable decrease in seroprevalence to 5.3% in the TPE arm representing a 47% reduction in seroprevalence.

11.4 Secondary outcome on feasibility - Coverage

For this study, coverage for each intervention is defined as follows:

- Investigation coverage – Proportion of eligible cases investigated out of eligible cases reported in the Rapid Reporting System
- Intervention coverage (Both TPE/RACD) – Proportion of eligible participants enrolled per intervention (up to 25 per intervention) out of the number of eligible residents within 500 meters of the index cases household (up to 25 per intervention)
- TPE – Proportion of people eligible for the intervention who took the first dose of AL (up to 25 per intervention) out of the number of eligible residents within 500 meters of index case household (up to 25 per intervention)
- RAVC – proportion of households receiving spraying (up to seven per intervention) out of the number of households within 500 meters of the index case (up to seven per intervention)

- Index case coverage – proportion of eligible participants receiving intervention in the index household out of the number of eligible residents of the index household.

People eligible for all arms of the study include all people who live in one of the households closest to the index household, or who are recorded as having stayed overnight there at least one night in the past four weeks and are present during the intervention. If the intervention team goes beyond the closest six households from the index case, residents of all houses approached to be part of the intervention will be included in the "eligible population" and will become part of the denominator. Households may be approached up to 500m from the index case household, if two visits have been made, all households within 500m approached and 25 people have not been enrolled, then the intervention is finished.

Total population of Target Areas will be based on total population recorded during the 2014-2015 geographical reconnaissance.

For the feasibility outcome measure of coverage, the goal coverage of 80% for the different interventions is based on modelling data and experience from settings that have successfully interrupted transmission in the setting of presumptive treatment. If our hypothesis is correct and estimates of incidence in the TPE arm are accurate, approximately 78 index cases will be identified and 1,961 people will be treated in the TPE Target Areas.[8,36] If the actual coverage is 80%, we would have a 95% confidence interval between 78% and 82% with this sample size. For the RACD and RAVC interventions, we will be powered to measure 80% coverage, as the number of people that receive RACD or RAVC will be higher than received for TPE.

11.5 Secondary outcome on feasibility – Adherence to AL administered in RACD and TPE

Adherence to medication will be measured by a pill count during follow up visits in all participants receiving medication in the RACD arm and in a selection of participants in the TPE arm see Table 7. We expect that 26 EAs in the TPE arm will have at least one index case, and at least 25 people will be assessed per Target Area (26*25=650), for a total sample of 774 people (see Table 7). If the actual adherence were 80%, we would have a 95% confidence interval between 77% and 83% with this sample size.

Table 7. Sample sizes for primary and secondary outcomes

Outcome	**Result***	**Effective Sample Size** (# of subjects unless otherwise indicated)
Primary aim		
Cumulative Incidence	18.81/1000 (RACD) vs. 7.84/1000 (TPE) and 7.84/1000 (RAVC) vs. 18.81/1000 (no RAVC)	15,456
Secondary aims		
Effectiveness		
Exposure (seroprevalence)	10% (RACD) vs. 5.3% (TPE) and 10% (no RAVC) vs. 5.3% (RAVC)	4,860 (does not include index cases)
Infection prevalence	n/a	4,860 (includes index cases)
Feasibility		
Coverage	80% (95% CI: 77%-83%)	5,279
Adherence	80% (95% CI: 77%-83%)	774
Prevalence of SAEs	n/a	5,279
Acceptability	n/a	5,279
Cost	n/a	10 Target Areas/arm

*For most secondary outcomes, power calculations were not performed; however, effective sample size is shown

11.6 HS RDT evaluation – To measure infection prevalence and the diagnostic accuracy of HS RDT

For the purpose of the HS RDT evaluation, with a sample size of 5,040 we will have more than 80% power to detect a 4% point prevalence of malaria infection by HS RDT, with a precision of 10%. To measure the

diagnostic accuracy of HS RDT using HRP II concentration or qPCR as a gold standard, we will have more than 90% power to measure a sensitivity of 65 to 99% with a precision of 10%, and a specificity of 91-99% with a precision of 1%.

11.7 Analysis

Primary Analysis and Missing Data

One-way frequency tables for all categorical variables and distributions, ranges, and outliers for continuous variables will be generated to perform range checks, quantify the amount of missing data, and generate descriptive findings that will characterize EA and Target Area characteristics in the study population. These analyses will be stratified by intervention group (i.e., TPE vs RACD and RAVC vs no RAVC) and we will describe the equality of group covariates at baseline. Although we expect the randomisation to produce balanced covariate structures, we will consider methods of adjustment to balance baseline covariates should there be differences between the arms.

Interim Analysis

After the first transmission season of the trial an interim analysis will be performed to determine progress and whether sample size will likely be met in the second year of the trial.

Primary Analysis (incidence)

For the primary analyses of the four study arms, there will be three major comparisons of incidence: between the TPE and RACD arms (28 EAs will receive TPE and 28 RACD), between RAVC and non RAVC arms (28 EAs each) and between the arm receiving TPE and RAVC (14 EAs) and the arm receiving RACD with no RAVC (14 EAs). For the primary comparisons, we will follow an intention-to-treat (ITT) approach. The null hypothesis is that there are no differences in incidence between study arms (all rate ratios = 1). We hypothesize that incidence will be reduced by 50% by TPE and 50% by RAVC, with a combined multiplicative reduction in the arm receiving both interventions (RR 0.25). For the primary ITT analyses, estimates of effect of each intervention will be estimated adjusting for the presence of the other intervention (i.e. the TPE vs. RACD analysis would be adjusted for the presence of RAVC), but without adjusting for any other co-variates. Outcomes will be assessed at the individual level.

Because of the clustered nature of the data, our modelling approach will adjust for correlation of observations by EA for analyses using the overall sample and by both EA and Target Area for analyses using the Target Area sample. Generalized estimating equations (GEE) will be used to perform the proposed primary analyses. GEE accounts for the correlation of persons within clusters and EAs. GEE estimates are consistent even if the correlation structure is incorrectly specified, though GEE's statistical efficiency improves as the working correlation structure more closely approximates the actual correlation structure. Thus, several working correlation structures suitable for the study's design will be considered (e.g., unstructured, Autoregressive order 1, exchangeable). The Quasi-Akaike Information (QIC) statistic will be used to select the final working correlation structure. Robust Huber-White "sandwich" standard errors will be used to obtain correct inferences even if the chosen correlation structure remains slightly mis-specified. Alpha will be set at 0.05 for all planned comparisons.

Subgroup analyses

Although power is limited by the constraints of the total number EAs in the study area, we will describe summary measures of incidence and intervention effects for some specific subgroups of interest within our study area population, such as members of each gender and age group, migrants, children, and those living in particular areas.

Secondary analyses

If the preliminary analyses reveal an imbalance in the baseline covariates between the TPE vs RACD arms, and RAVC vs non-RAVC arms, a second set of models will be run for all primary analyses. Adjusted models will reweight the data (through inverse probability weighting, or targeted minimum loss based estimation) to recover effect estimates that reflect an equal distribution of baseline covariates.

Assessments of secondary outcomes will be conducted using GEE techniques to account for the clustered nature of the data collection, as described above. Secondary analyses for prevalence and seroprevalence are restricted to people in Target Areas who participate in the cross-sectional endline survey. For analyses of outcomes in the Target Area sample, clustering by both EA and Target Area will be accounted for in the modelling approach. Planned secondary analyses and hypotheses are as follows

Hypotheses regarding the effectiveness of the different interventions:

1. Comparison of seroprevalence using antibodies to markers of recent exposure. Upon analysis of samples collected in mid-2017, we expect to find lower seroprevalence in areas receiving TPE than in those receiving RACD, as well as those receiving RAVC vs no RAVC.

   Comparison of prevalence of malaria infection. We expect prevalence to be lower in Target Areas receiving TPE than in those receiving RACD, as well as those receiving RAVC vs no RAVC.

Planned analyses of operational feasibility and expected findings:

1. Coverage of the intervention. Coverage of the different interventions will be assessed using several different approaches depending on intervention arm. The numbers and proportion of the following intervention coverage indicators will be calculated by arm:
   a) Eligible cases investigated out of the eligible cases reported in the rapid reporting system;
   b) The participants completing finger prick testing (RACD arm), or receiving at least the first dose of medication (TPE arm) up to 25 per intervention out of the number of eligible residents living within 500 meters of the index case household up to 25 per intervention;
   c) Participants receiving AL per intervention (up to 25 per intervention) out of the number of eligible residents within 500 meters of the index case household (up to 25 per intervention);
   d) Households receiving spraying (RAVC arm) up to seven out of the index case and six closest households or all within 500 meters of the index case household; and
   e) Index case household members completing finger prick testing (RACD arm) or receiving at least the first dose of medication (TPE arm) up to 25 per intervention out of the number of eligible residents of the index household.

The proportion of the people living in Target Areas around an index case that receive each intervention is expected to be 80% with a 95% confidence interval from 77% to 83%.

2. Adherence to medication. In the subsample of Target Areas in the TPE arm and in all participants receiving medication in the RACD arm, we will assess the adherence to the three-day regimen of AL using a pill count. We expect adherence to be 80%.
3. Safety of the treatment/additional IRS. The number and percent of people experiencing an adverse event will be recorded by study arm. We expect that medications and insecticide will be safely administered with few or no serious adverse events related to the intervention.
4. Acceptability of the intervention. Interviews and focused group discussions will be audio-recorded then transcribed and translated with a brief summary written for each interview. Transcripts will be coded and to identify major themes associated with the acceptance. We will describe facilitators and barriers to these strategies with the goal of identifying the most acceptable way to engage the community in malaria elimination.
5. Costs per intervention event and per population. Detailed costing will be performed in 10 Target Areas per arm. We expect that costs per intervention event and per population for implementing TPE will be no higher than for RACD.

12.0 Ethics considerations

12.1 Consent

The following consents will be conducted:

Table 8. Informed consent overview

Subject/Activity	Informed consent covers	
Index case, Case investigation	Informed consent for DBS collection None needed for RDT or case investigation form as they are usual MoHSS protocol.	
Resident Enrolment, Intervention All residents of Target Areas	**RACD**	*At enrolment*: • Brief questionnaire and GPS mapping. • RDT test, treatment if positive, referral to health facility if indicated • Storage of blood with DBS. *Post intervention:* Potential focus group discussion
	TPE	*At enrolment:* • Brief questionnaire and GPS mapping. • 3 day course of antimalarial treatment by modified DOT. • Additional IRS if in RAVC arm • *Post intervention:* • Potential pill count. • Potential focus group discussion
	RAVC	*At enrolment:* • Brief questionnaire and GPS mapping • Assistance moving household items • Spraying of walls and ceiling of all sleeping structures
Serology Follow-ups Index cases from Phase I case-control study; Secondary cases and some RDT-negative controls from RACD EAs.	• *At 6-12 and 12-24 months after diagnosis (Note: The study team will seek consent at both of these visits)* • Follow-up blood testing with RDT, treatment if positive, & referral to health facility if indicated (see Protocol) • Storage of blood with microtainer and DBS.	
Resident Enrolment, Endline survey All residents of study Enumeration Areas	*At endline survey study:* • Brief questionnaire and GPS mapping • Follow-up blood testing with RDT, treatment if positive, & referral to health facility if indicated • Blood testing with new highly sensitive RDT • Storage of blood with DBS and microtainer.	
Acceptability Assessment Participants selected for inclusion in Acceptability Assessment	Participation in qualitative interview and/or focus group after intervention	

Written informed consent will be obtained from the household members and neighbours eligible for the study. For the qualitative assessment, verbal informed consent will be obtained for study participants. For the field procedures (survey, blood testing, and follow-up visits), people will be asked to consent each time they are eligible to be part of the study. Consent will not be required for collection of de-identified, used RDTs from health facilities inside and outside of the Zambezi region, if this collection is deemed feasible.

Consent will be conducted in the participant's house prior to study activities. Consents may be collected from all members of the household at once. Parents will be able to sign one form to consent for themselves and all of their participating children (under18 years old) at once. Each additional adult member of the house will sign separate consent forms. Each minor (12-17 years old) will sign a separate assent form.

Informed consent will be conducted in SiLozi, the most universal local dialect, or English, per participant preference, and an interpreter will be used if necessary. Consent forms will be available in English and SiLozi, and if the consent is conducted in neither of these, the language of consent will be documented and a witness who speaks the same language will be asked to sign to confirm the informed consent process. If the

participant is unable to read or write, an X will substitute for a signature. All signatures will be collected on the tablet and stored electronically, linked to the related questionnaire.

As part of the informed consent process, study personnel will assess participants' understanding of the study procedures that were explained by using a checklist comprised of key components of the study. Participants who pass will be allowed to sign the written consent form. If the participant does not pass, the consent discussion will be repeated, before asking for a signature. In this case, the consent form will be read again, focusing on areas where understanding was limited, and encouraging the subject to ask questions. Up to five attempts will be permitted per participant. If, despite five consecutive attempts (each incorrect one followed by the team's correction with explanation), the participant still has not answer a minimum number of questions correctly, then he/she will not be allowed to take part in TPE.

12.2 Management of sick participants

During the intervention, individuals with complicated malaria or symptoms requiring further evaluation will be referred for evaluation at the nearest health facility.

12.3 IRBs

The study protocol, as well as all informed consent documents and future revisions will be reviewed and approved by corresponding IRBs before the study launch. The University of California, San Francisco CHR will provide the primary review. The London School of Hygiene and Tropical Medicine will also provide a full review, with the knowledge that UCSF is also reviewing. The MoHSS and UNAM will conduct protocol reviews. No outside IRB will rely on the UCSF CHR review.

Site Information:

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London School of Hygiene and Tropical Medicine
Keppel St
London, UK WC1E 7HT

12.4 Governance

Namibia Malaria Elimination Research Partnership Steering Committee (NAMEP)

Role of the Steering Committee

The role of Steering Committee will be to support the implementation of research, interpretation of findings, and broader dissemination of findings to produce national and international impact. By making recommendations, the Steering Committee will provide oversight to ensure that the research is well coordinated, scientifically and ethically sound, and in line with the MoHSS' goals for malaria elimination in Namibia. Not all committee members are expected to be directly involved in the project outside of protocol review and annual meetings. {See Appendix R for Terms of Reference}

Membership of Steering Committee

The Steering Committee for NAMEP will provide guidance and oversight for this research. The NAMEP Steering Committee was established in April 2014 to support Namibia in its goal to eliminate malaria. Members of the Steering Committee are senior representatives of the institutions collaborating to implement the NAMEP program, which involves working to develop and test innovative surveillance and

response strategies in Zambezi region. The NAMEP Steering Committee includes people from the University of California, San Francisco, the Ministry of Health and Social Services, National Vector-borne Diseases Control Program, The University of Namibia, Multidisciplinary Research Centre, The London School of Hygiene and Tropical Medicine, the Clinton Health Access Initiative, Witswatersrand University, and the Novartis Foundation.

Activities of the Steering Committee

The Steering Committee will meet once yearly in Namibia to review and provide recommendations to this project. In addition, they will participate in teleconferences one to two times a year to provide additional input on project preparation, implementation, and progress. International members will be encouraged to join the annual Steering Committee meeting in person, however may join by teleconference if schedules limit travel to Namibia. Steering Committee members will also have ongoing interactions with study team members on an as needed basis.

12.5 Potential Limitations

Malaria declines: There is a possibility that the number of cases detected in Zambezi could drop significantly and impact our ability to collect sufficient data to draw conclusions about malaria epidemiology in Zambezi region. However, given the current assumptions and malaria incidence, which was 19.5 cases/1,000 residents from 2013 to 2014, this is unlikely to be a problem. However, if this occurs, and we would no longer be powered to assess the primary aim, the study could expand to additional health facilities within Zambezi region or extend another year. These issues will be addressed in the interim analysis.

Malaria increases: Due to climate, intrinsic disease dynamics, or regional increases, or changes in MoHSS implementation of standard malaria prevention strategies, the malaria burden in Zambezi region could increase over the study period. This occurred during the 2016 season, significantly affecting the study. The malaria burden in regions of Namibia near Zambezi region, as well as malaria in areas of Angola, Zambia, and Botswana that border the region will influence local malaria incidence. Increases in malaria burden in Zambezi region and surrounding areas will mean that health facility staff will experience a higher case load than they are currently, perhaps leaving them less time to complete case investigation forms and participate in any other study activities. The program will monitor ongoing malaria incidence and completion of tasks necessary for the project and will adjust staffing accordingly. Additionally, it may be necessary to increase the threshold for an intervention response (e.g. > 1 incident case). If this change is made, the same change will be made to all study arms and therefore should not affect the comparability of the arms as long as there are enough teams to maintain sufficient coverage.

Implementation of a drug change partway through the study: The drug regimen for both TPE and RACD will be based on the national first line treatment for uncomplicated *Pf* malaria. At present, the first line treatment is AL. A new policy was approved that includes the use of single dose PQ with AL for its anti-gametocidal properties. As our study is nested within operations of the NVDCP, we may change the drug regimen for RACD to AL+PQ partway through the study. However, we do not anticipate that this will affect our ability to distinguish impact between the study arms of the trial. As the study should have similar numbers of index cases in all arms of the study, the transmission blocking impact on index cases will be balanced. In the event that the use of PQ has a greater than expected impact on transmission in the RACD arm, we may need to increase the sample size of the study by lengthening the study period.

Data quality and management: Data collection will occur in various locations by different team members and there is potential for inconsistencies. However, all team members will receive comprehensive training and supervision to ensure data quality. To ensure data quality the Data Manager will sample a proportion of case investigation forms to ensure that they are complete and that data are entered correctly into the database and the SDSS. Additionally, occasional sampling of case registers will occur to ensure that all malaria cases are being reported to the Surveillance Officer.

Barcode labels will be used to link blood samples to data collection forms. The Site Manager and Surveillance Officer will provide oversight to maintain study procedures. All team members will receive regular updates on interim study findings to promote ownership of the study and maintain interest.

Laboratory capacity LAMP, PCR, ELISA, and genotyping are relatively straightforward procedures and we do not expect the laboratory technologists to have any difficulty, as they already have experience with these methods. However, if it is not possible to perform these procedures reliably in either Zambezi region at the MoHSS reference laboratory or in Windhoek at the UNAM laboratory, we will transfer samples to the UCSF laboratory for testing.

13.0 Timeline

Expected outcomes and related activities	Year or Quarter				Milestones
	Year 2 1/-12/2015	Year 3 1/-12/2016	Year 4 1/17-12/17	After Year 4	
Study preparation					• Develop, review, and finalize work plan & protocol. In-country review; incorporate feedback into protocol. Finalize protocol. • Randomize EAs. Sensitization of participating EAs. • Complete & submit applications to IRBs. • Finalize & translate informed consents. • Finalize questionnaires.
Trainings					• Finalize & translate training materials. • Conduct trainings for lab and field personnel.
Study intervention					• Finalize SOPs for field procedures. • Order supplies (drugs, insecticide, field supplies). • Field team conducts case investigations & deploys RACD or TPE +/-RAVC.
Adverse event monitoring					• When adverse events occur, collect additional data to assess causality. • Prepare reports of serious adverse events.
Data collection: Laboratory assessment					• Finalize SOPs for lab procedures. • Order supplies. • Ongoing blood surveys for LAMP/PCR in RACD arm.
Data collection: outcome measures					• Perform routine surveillance for incidence data. • Collect & coordinate the endline survey, expected mid 2017 (blood samples for infection prevalence and serology). • Collect operational feasibility outcome measures – coverage, safety (adverse event monitoring above), costs, and adherence.
Data collection for Acceptability study, qualitative assessment					• Finalize SOPs for qualitative assessment of acceptability. • Field team performs FGDs and in-depth interviews with study participants and key stakeholders.
Project Monitoring					• Develop and finalize SOP for monitoring project data. • Database check-ins. • Coordinate and hold annual and ad-hoc meetings of the DSMB and the Advisory Committee.
Preliminary data analysis					• Develop and finalize SOPs for data analysis. • Preliminary analysis on coverage, acceptability, cost-effectiveness, safety, and incidence,
Final data analysis					• Final analysis of coverage, prevalence of SAEs, acceptance, cost-effectiveness, incidence, parasite prevalence, seroprevalence, etc.
Prepare final manuscripts and reports					• Prepare manuscripts for publication. • Review with collaborators, incorporate feedback into manuscripts.

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15.0 Appendices

A. Summary of Phase I surveillance and capacity building activities
B. Study information for stakeholders
C. Index Case Investigation Form
D. Community Level Investigation Tracking Form
E. Household Level Questionnaire
F. Individual Level Questionnaire
G. Modified DOT Record
H. Pill Count and Adverse Events
I. AL weight-based dosing
J. Modified DOT Dosing Schedule
K. Qualitative Key Informant Interview Guide
L. Qualitative Focus Group Discussion Guide
M. Adverse Events SOP
N. MoHSS Serious Adverse Event Report Form
O. WHO Toxicity Grading Scale
P. Data and Safety Monitoring Board Terms of Reference
Q. Consent Forms
R. Steering Committee Terms of Reference
S. Serology Sub-study Questionnaire
T. XS Survey Household listing and clinical forms
U. XS Survey Household questionnaire
V. XS Survey Individual questionnaire