REACTIVE TARGETED PARASITE ELIMINATION (TPE)

Study Title: Evaluating the effectiveness and feasibility of reactive targeted parasite elimination vs. reactive case detection as a community-level intervention in response to a passively identified index case in Swaziland

Funded by: The Bill and Melinda Gates Foundation

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Table of Contents

Study summary 5

Study personnel and institutions 6

Principal Investigators 6

Other Key Personnel and Collaborators 6

Study members and responsibilities 10

Administrative contacts 14

Institutional review boards 14

Primary Funder 15

Abbreviations & acronyms 16

1 Background 17

1.1 Malaria in Swaziland 17

1.2 Challenges for Malaria Elimination 17

1.3 Reactive case detection (RACD) 17

1.4 Targeted parasite elimination (TPE) 19

1.5 RACD vs. reactive TPE 19

1.6 Drug regimens 20

2 Rationale 21

3 Study aims 23

4 Study design & methods 24

4.1 Overview 24

4.2 Study site and study population 24

4.3 Randomization of localities (clusters) 24

4.4 Target Areas 28

4.5 Inclusion and exclusion criteria 30

5 Baseline Preventative Interventions – LLINs and IRS 31

6 Enrollment 31

6.1 Sensitization 31

6.2 Identification of Target Areas (through immediate case notification and Case investigation of the index case) 32

6.3 Informed consent 32

7 Study intervention 33

7.1 Household-level questionnaire 33

7.2 RACD arm - Perform RDT and refer secondary cases to health facilities 34

7.3 TPE arm - Administration of DP 34

7.4 Management of sick participants 35

7.5 Adherence assessment 35

8 Adverse event monitoring 37

8.1 Overview 37

8.2 Definitions 37
8.3 Passive identification of SAEs 37
8.4 SAE report forms 37
8.5 Expedited reporting of SAEs and SUSARs 38
8.6 Management of participants with SAEs 38
9 Follow-up surveys 38
9.1 Overview 38
9.2 Follow-up blood survey at 6-9 months 38
9.3 End-line survey (at the end of the study, expected mid 2017) 39
10 Acceptability Assessment 39
10.1 Background and Rationale 39
10.2 Aims of the Acceptability Assessment 40
10.3 Methods for the Acceptability Assessment 40
11 Cost-effectiveness assessment 42
12 Laboratory procedures 42
12.1 Rapid diagnostic tests 42
12.2 Filter paper sample collection 42
12.3 Microtainer blood collection 43
12.4 Antibody and DNA extraction 43
12.5 LAMP 43
12.6 PCR 43
12.7 Genotyping 43
12.8 QT-NASBA for gametocytes 43
12.9 ELISA 43
12.10 Sample storage for future studies (for research purposes only) 44
13 Data management 44
13.1 Quality assurance & quality control 44
13.2 Records & storage 44
14 Statistical issues 44
14.1 Study population 44
14.2 Outcome measures 46
14.3 Estimates of study power 46
14.4 Analytical plan 49
15 Advisory Committee 51
15.1 Role of the Advisory Committee 51
15.2 Membership of Advisory Committee 51
15.3 Activities of the Advisory Committee 51
16 Data and Safety Monitoring Committee 52
16.1 Data and Safety Monitoring Committee 52

16.2 Meetings 52
16.3 Stopping guidelines 52
17 Ethical considerations 52
17.1 Institutional review boards 52
17.2 Informed consent process 52
17.3 Risks and discomforts 53
17.4 Compensation 54
18 Timeline 55
19 References 56

Appendices

Appendix A: Study information for stakeholders
Appendix B: Index case immediate notification form
Appendix C: Index case, Case investigation form
Appendix D: Unsuccessful Case Investigation
Appendix E: Informed Consent Forms for Resident Enrollment, Intervention, RACD Arm
Appendix F: Informed Consent Forms for Resident Enrollment, Intervention, TPE Arm
Appendix G: Neighborhood information
Appendix H: Household level RACD questionnaire
Appendix I: Individual level RACD questionnaire
Appendix J Household level TPE questionnaire
Appendix K: Individual level TPE questionnaire
Appendix L: Informed Consent Forms for 6-9 month follow-up visit
Appendix M: 6-9 month follow-up visit questionnaire
Appendix N: Informed Consent Forms for Resident Enrollment, End-line Survey
Appendix O: End-line survey household questionnaire
Appendix P: End-line survey individual questionnaire
Appendix Q: DP weight-based dosing guidelines
Appendix R: Modified DOT dosing schedule
Appendix S: Serious adverse event report form
Appendix T: WHO Grading for Determining Severity of Adverse Events
Appendix U: Informed Consent Forms for Acceptability Assessment
Appendix V: Qualitative questionnaires for the Acceptability Assessment – Individual Interviews with Refusers
Appendix W: Qualitative questionnaires for the Acceptability Assessment – Focus Groups with Participants
Appendix X: Qualitative questionnaires for the Acceptability Assessment – Focus Groups with Malaria Surveillance Team
Appendix Y: Swaziland Malaria Elimination Advisory Group (SMEAG) Terms of Reference
Appendix Z: TPE Safety Monitoring Committee Terms of Reference

Study summary

Title	Evaluating the effectiveness and feasibility of reactive targeted parasite elimination (TPE) vs. reactive case detection (RACD) as a community-level intervention in response to a passively identified index case in Swaziland
Study design	Cluster randomized controlled trial
Aims	**Primary aim:** To compare the impact of TPE versus RACD on malaria incidence. **Secondary aims** **Effectiveness:** **1.** To compare the impact of TPE versus RACD on seroprevalence. **2.** To compare the impact of TPE versus RACD on prevalence of infection. **3.** To compare the impact of TPE versus RACD on proportion of imported incident cases. **4.** To compare the impact of TPE versus RACD on time to first post-intervention incident local case. **5.** To compare the impact of TPE versus RACD on transmission potential as measured by relatedness of infections by microsatellite genotyping. **Feasibility:** 1. To determine the feasibility of reaching 80% coverage for TPE versus RACD. 2. To evaluate the safety of TPE versus RACD. 3. To compare the acceptability of TPE versus RACD. 4. To compare the costs and cost-effectiveness of TPE versus RACD. 5. To measure the adherence to modified DOT with DP in the TPE arm.
Study site	Eastern endemic region of Swaziland, a very low endemic malaria elimination setting. A total of 287 health facilities and their catchment areas are located in this area.
Time frame	September 2015 until two transmission seasons completed (mid-2017)
Cluster or unit of randomization	At risk localities will be randomized to either TPE or RACD using a block stratified randomization based on risk rank (1-3) and population
Target area	For TPE localities: Neighborhood of individuals residing within 200m of an index case detected in passive surveillance. Individuals residing immediately beyond 200m will be included if a minimum of 30 individuals are not enrolled within 200m. For RACD localities: Neighborhood of individuals residing within 500m of an index case detected in passive surveillance.
Intervention	All individuals residing in study localities will receive vector control preventative measures as per program. In the TPE arm, all individuals in the Target Area will receive dihydroartemisinin-piperaquine (DP) once daily for 3 days with the first dose taken no later than 5 weeks from the index case presentation (goal within one week). Individuals in RACD Target Areas will be tested by RDT and taken to the nearest health facility for treatment as per program operating procedures.
Evaluation methods	The primary outcome measure of incidence will be obtained routine surveillance data. Secondary outcomes will be measured through Target area-level surveys: **1) Blood surveys.** At the time of enrollment of a new Target area in RACD arm and at study conclusion in both arms (LAMP, QT-NASBA, serology, genotyping). DBS collected in incident cases as part of routine surveillance will also be utilized for genotyping. **2) Feasibility measurements:** Coverage of RACD or TPE in the target population, serious adverse event (SAE) reports, costing of every 10th RACD and TPE event, pill count in TPE arm. **3) Acceptability assessment.** Focus group discussions with TPE study participants and RACD/TPE surveillance team members.
Sample size	The sample size is based on the number of study localities that experienced at least one incident case of malaria in the previous season. Within 77 randomized localities, we expect that 63 localities will have an incident case of malaria and receive an intervention. For the primary objective, we hypothesize that TPE will be more effective than RACD. At the current sample size the study is powered to detect a difference in cumulative incidence if incidence in the TPE arm is reduced 50% compared to the RACD arm. Incidence will be measured at the locality level and among the at-risk population, or all individuals in an enumeration area (EA) where at least one case was identified (expected to be approximately 55928 among total study population of 211,189, or a harmonic mean of 656 per locality (41,328 effective population). Secondary outcomes of seroprevalence and prevalence will be measured on individuals residing in Target Areas (total N=5400) with a harmonic mean of 60 persons receiving intervention per locality (3780 effective population).
Primary outcome	Incidence of malaria cases
Secondary outcomes	1) Seroprevalence by ELISA 2) Prevalence of infection 3) Proportion of imported to locally acquired incident cases 4) Time to first post-intervention incident local case 5) Transmission potential as measured by microsatellite genotyping 6) Coverage of the intervention: proportion of the target population that receives a finger prick in the RACD arm or that receives an initial dose of DP in the TPE arm (intention to treat analysis) 7) Adherence to DP in TPE arm. 8) Prevalence of serious adverse events (SAEs) related to treatment 9) Acceptance as evaluated by refusal rates and a qualitative assessment

	10) Cost per intervention episode, per case averted

Study personnel and institutions

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Study members and responsibilities

Principal Investigators

Michelle Hsiang, Principal Investigator: Responsible for oversight of the project, study design, data collection management, ethical approval, oversight of laboratory procedures, data analysis, and report and manuscript writing.

Simon Kunene, Co- Principal Investigator: Responsible for oversight of the project with a focus on coordination, and management of Global Fund/NMCP supported aspects of the project. Will provide input on study design, data analysis and report and manuscript preparation. Will ensure that study findings impact future program implementation as indicated.

Roly Gosling, *Co- Principal Investigator:* Provide support to oversight of the project with focus on study design, data collection management, safety monitoring, data analysis, and report and manuscript preparation. Will align study activities with others involving the Malaria Elimination Initiative, UCSF Global Health Group.

CHAI

Nyasatu Ntshalintshali, Study Supervisor: Based in Swaziland at the CHAI office, will supervise all aspects of the project implemented in Swaziland (including coordination, field work, lab work, administration) and maintain relationships between GHG, NMCP, MoH, Swaziland Laboratory Health Services, and CHAI. Will report to Charlotte Lejune (CHAI Swaziland Country Director) and Deepika Kandula. Will directly support collaboration between GHG, GHG-supported study staff, NCMP, and CHAI. Will support tablet development and maintenance in collaboration with NMCP Information Technology (IT) Officer. Will serve as focal point for in-country IRB. Participate in analysis and preparation of reports and manuscripts, and support translation of study findings into program implementation as indicated. Will help align study work with other CHAI-supported malaria work in Swaziland and elsewhere.

TBD: Based in Swaziland at the CHAI office, the Study Manger will provide day to day management all aspects of the project implemented in Swaziland (including coordination, field work, lab work, administration) and maintain relationships between GHG, NMCP, MoH, Swaziland Laboratory Health Services, and CHAI. Will report to Charlotte Lejune (CHAI Swaziland Country Director) and Nyasatu Ntshalintshali. Will directly support collaboration between GHG, GHG-supported study staff, NCMP, and CHAI. Will supervise Research Associate as well as UCSF Research Specialist when in Swaziland. Will support subcontract development and associated reporting. Will participate in analysis and preparation of reports and manuscripts, and support translation of study findings into program implementation as indicated. Will help align study work with other CHAI-supported malaria work in Swaziland and elsewhere.

Bongani Dlamini, Research Associate: Responsible for overall study coordination on the group. Will report to Nyasatu Ntshalintshali. Will supervise Field Coordinator and Drivers. Will support development of study SOPs. Will work closely with the NMCP surveillance and vector management team to ensure that study goals and procedures are aligned with those of NMCP. Coordinate trainings and re-trainings. Coordinate Pharmacovigilance and Adverse Drug Reactions Committee. Responsible for ordering supplies (including laboratory supplies) and accounting. Will assure to security and maintenance of study materials and blood samples. Will manage transportation. Will organize and lead weekly skype conferences as well as biannual meetings to include all study personnel and prepare meeting minutes. Work with Study Supervisor, Study Manager, and Principal Investigators to troubleshoot when challenges arise. Will help host and make arrangement for team members visiting from UCSF.

Field Coordinator: Responsible for coordinating field data collection. Will work closely with NMCP Field operations focal point to ensure prompt response to cases for RACD or TPE and adherence to study protocols. Will ensure that procedures are aligned with standard NMCP surveillance and response procedures. Coordinates use of study vehicles. Will supervise field staff. Will coordinate all activities with Rural Health Motivators. Will coordinate and help implement data collection for the acceptability and cost-effectiveness study.

Study Physicians: Responsible for overseeing safety aspects of the study. Will review records of DP or AL administration as well as reports on adverse events. Will be on call to address adverse events as they occur. Will ensure that alternate medical care is available when not available. Will participate in and lead safety related portions of the Pharmacovigilance and Adverse Drug Reactions Committee.

NMCP

Nomcebo Mkhonta, Chief Surveillance Officer, Study Surveillance Focal Point: Oversees surveillance team and will provide support to Study Supervisor and Research Associate so that field work is completed thoroughly and accurately. Will work closely with the Study Research Associate and Field Coordinator to ensure that case investigations, and RACD or TPE are performed in a timely manner and according to

protocol. Will help troubleshoot as issues arise. Will help align study with standard programme procedures. Will review data weekly with Data Manager and UCSF Research Specialist, ensuring data quality and completeness. Will join for biannual update meetings and participate in weekly calls as needed.

Calsile Malambe, Surveillance Officer, Study Field Operations Focal Point: Oversees NMCP surveillance agents and serves as the focal point for field operations particularly in Lubombo. Will work closely with Study Research Associate and Field Coordinator to ensure that case investigations, and RACD or TPE are performed in a timely manner and according to protocol. Will help align study with standard program procedures. Will review field operations with the Field Coordinator and Research Associate on a weekly basis ensuring data quality and completeness.

Swaziland Laboratory Health Services

Gugu Maphalala, Principal Technologist (Research): Oversees laboratory technicians. Will ensure that study laboratory procedures including storage of samples and performing of laboratory assays, are integrated into regular workflow and structure of National Reference lab. Will support technologists and UCSF Research Specialist to ensure proper functioning of equipment and maintenance of laboratory space.

Molecular Technologist: In close collaboration with other laboratory staff in in Swaziland Laboratory Health Services, will perform LAMP and ELISA on DBS collected through surveillance as well as for the TPE study. Will maintain blood samples in the lab, assure that adequate stocks of laboratory supplies are maintained, and liaise with NMCP or Research Associate to order new supplies as needed. Will enter results into database. Will work closely with UCSF Research Specialist to ensure timely and quality sample processing, and to trouble shoot as needed. Will participate in telephone conferences to share results and troubleshoot. Will supervise Assistant Molecular Technologist and report to the Head of the Molecular Lab.

Assistant Molecular Technologist: Will perform LAMP and ELISA on DBS collected through surveillance as well as for the TPE study. Will support Molecular Technologist to maintain blood samples in the lab, assure that adequate stocks of laboratory supplies are maintained. Will enter results into database. Will work closely with UCSF Research Specialist to ensure timely and quality sample processing, and to trouble shoot as needed. Will participate in telephone conferences to share results and troubleshoot. Will report to Molecular Technologist and the Head of the Molecular Lab.

UCSF

Research Specialist: The UCSF Research Specialist will support study coordination while also leading data management, data analysis, and laboratory aspects of the project. The Research Specialist will be based at UCSF but also spend 3-6 months/year based at the CHAI Swaziland office, reporting to Michelle Hsiang, and also to the Study Manager when in country. Specific activities will be to: support development of protocol, lead SOP writing with guidance from PIs, Study Supervisor, Study Manager, and support from the Research Associate. Support Research Associate and Study Manager in field coordination. Help Research Associate coordinate field trainings and re-trainings. Lead laboratory trainings and re-trainings as needed. Manage and perform laboratory assays, working closely with Molecular Technologist and Assistant Molecular Technologist. Track progress of LAMP testing for surveillance samples (passive and active). Prepare study updates for Swaziland Laboratory Health Services leadership. Manage data with NMCP IT Officer, perform data cleaning and monitor data quality. Perform data analyses and prepare reports and manuscripts. Submit and maintain UCSF IRB.

Maxwell Murphy, UCSF laboratory manager: Will perform PCR, LAMP, serology, and genotyping at UCSF. Will support laboratory trainings and ordering of laboratory supplies. Will work with UCSF post doc to help troubleshoot when needed. Reports to Bryan Greenhouse. Will coordinate weekly meetings to review laboratory findings and plans.

Bryan Greenhouse, Collaborator: Will provide guidance to the project, particularly with regards with PCR and serology work, as well spatial analysis, overall data analysis and manuscript preparation. Will supervise Maxwell Murphy.

Mi-suk Dufour: Will provide support to study design, data analysis, and preparation of reports and manuscripts. Reports to Michelle Hsiang and will work closely with UCSF Research Specialist.

Kim Baltzell, Qualitative Research Scientist: Lead the study design, survey development and protocol writing for the Acceptability Assessment. May supervise a student or other study staff on the study coordination, SOP development, data collection, analysis, and writing of the project.

Ranju Baral, Economist: Lead the study design, protocol writing, and preparation of data collection tools for costing and cost-effectiveness study. Will support data analysis and writing of the project.

Grant Dorsey, Senior Advisor: Will provide high-level guidance to the project particularly with regards to study design, troubleshooting with data collection, interim and final data analyses as well as manuscript preparation.

Adam Bennett: Will provide input on study design and data analysis. Will align work with other surveillance and response activities of UCSF Global Health Group, Malaria Elimination Initiative.

Hugh Sturrock: Will provide support on GIS related aspects of the study including spatial analysis. Will align work with similar reactive surveillance studies in Namibia.

CHAI Global

Deepika Kandula, Collaborator: Through supervision of Nyasatu Ntshalintshali, will provide guidance on collaboration between UCSF GHG, CHAI, NCMP, and MoH. Will provide input on study coordination and translation of study findings into program implementation as indicated. Will help align study work with other CHAI-supported malaria work in Swaziland and southern Africa.

Justin Cohen, Collaborator: Will provide input on study design, data analysis and writing. Will help align work with CHAI- Global malaria elimination activities. Will help translate findings into policy level decisions.

Arnaud Le Menach, Collaborator: Will provide technical support to research activities. Will help align work with CHAI- Global malaria elimination activities. Will help translate findings into policy level decisions.

FIND

Iveth González, Collaborator: Will provide technical support to LAMP activities including troubleshooting, quality assurance, and interpretation of findings. Will provide linkages to other sites using LAMP. Will liaise with Eiken Chemicals regarding price negotiation and ordering of LAMP kits.

LSHTM

Chris Drakeley, Collaborator: Will collaborate on serology studies, particularly with regards to experimental design, troubleshooting, analysis and interpretation of results. Will also support antigen procurement and exchange of ideas from ongoing work in London and elsewhere.

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Abbreviations & acronyms

ACT	artemisinin-based combination therapy
AL	artemether-lumefantrine, Coartem
CHAI	Clinton Health Access Initiative
DBS	Dried blood spot
DOT	directly observed therapy
DP	dihydroartemisin-piperaquine, Eurartesim
EDTA	ethylene-diamine-tetra-acetic acid
EIR	Entomological Inoculation Rate
ELISA	enzyme-linked immunoabsorbent assay
FGD	Focus Group Discussion
FIND	Foundation for Innovative New Diagnostics
G6PD	Glucose-6-phosphate dehydrogenase
GEE	Generalized Estimating Equation
GPS	global positioning system
HH	Household
IRB	Institutional Review Board
IRS	indoor residual spraying
ITN	insecticide treated bednet
IPT	intermittent preventative therapy
ITT	intention to treat
LLIN	long-lasting insecticide treated bed net
LAMP	loop-mediated isothermal amplification
LSHTM	London School of Hygiene and Tropical Medicine
MDA	mass drug administration
MEI	Malaria Elimination Initiative
MoH	Ministry of Health
NMCP	National Malaria Control Program
OR	odds ratio
PI	Principal Investigator
PCR	polymerase chain reaction
Pan-LAMP	LAMP assay detecting all *Plasmodium* species
Pf	*Plasmodium falciparum*
Pf-LAMP	LAMP assay detecting *Pf* only
QTc	corrected QT interval
QT-NASBA	quantitative nucleic acid sequence-based amplification
RACD	reactive case detection
RDT	rapid diagnostic test, a point of care assay to diagnose malaria
RHM	Rural Health Motivator
RR	relative risk
SAE	serious adverse event
SLHS	Swaziland Laboratory Health Services
SMEAG	Swaziland Malaria Elimination Advisory Group
SNP	Single Nucleotide Polymorphism
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TPE	Targeted Parasite Elimination
UCSF	University of California, San Francisco
UCSF GHG	UCSF Global Health Group
UNICEF	United Nations Children's Fund
UNISWA	University of Swaziland
UTSW	University of Texas Southwestern

1 Background

1.1 Malaria in Swaziland

Swaziland is a small country in southern Africa that was the first country in sub-Saharan Africa to embark on an elimination campaign in 2008.[1]The country has made remarkable progress towards this goal, mainly through the roll-out of artemisinin-based combination therapies (ACTs), laboratory confirmation of all clinical cases using rapid diagnostic tests (RDTs), vector control using insecticide treated bednets (ITNs) and indoor residual spraying (IRS) in historically at-risk areas, health education, as well as an active surveillance program whereby household members and neighbors of index cases (individuals infected with *Plasmodium*) are screened using RDTs and treated if positive. The population at risk is 285,972, representing 30% of the population that lives in the Eastern endemic region (Figure 1). The number of locally acquired cases fell from 186 in 2010-11 to 84 in 2012-13. Imported malaria from Mozambique on the northeastern border is a challenge with the proportion of imported cases increasing from 51 to 71% during the same time period. The main parasite is *Plasmodium falciparum (Pf)* and the main vector is *A. arabiensis*. The high malaria transmission starts in November and ends in June; however, in recent years, the burden of local cases does not follow a seasonal pattern (Figure 2).

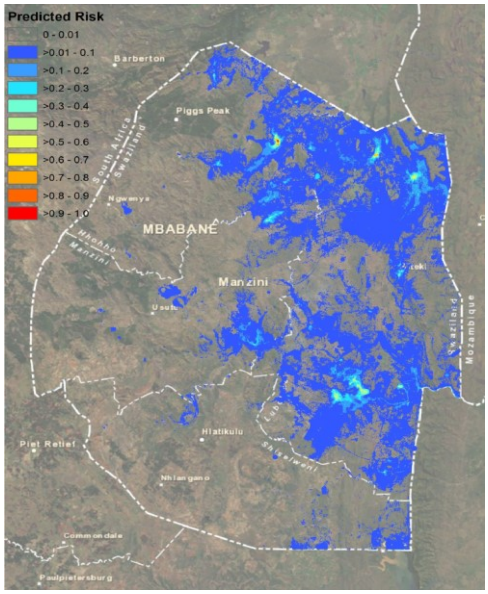

Figure 1. Predicted risk of local case

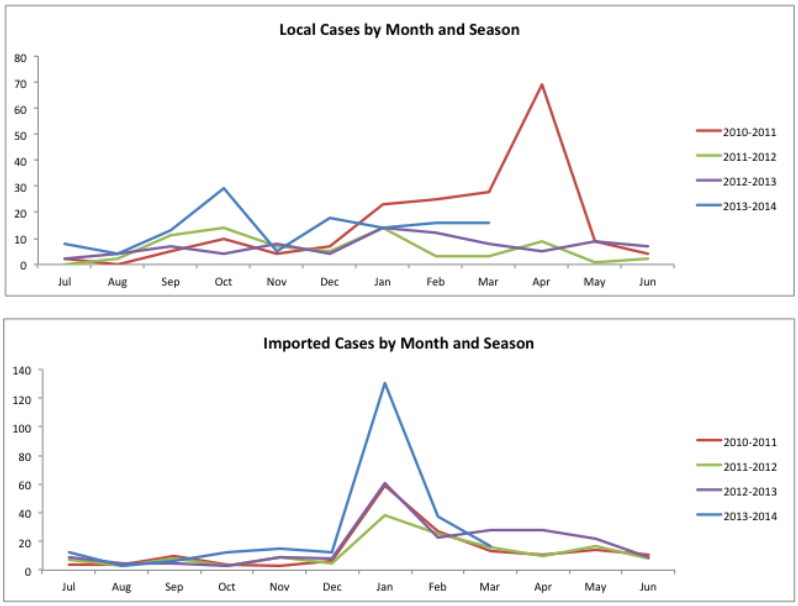

Figure 2. Local and Imported cases by month and year

1.2 Challenges for Malaria Elimination

In recent years, many countries like Swaziland have experienced reductions in malaria transmission in association with the scaling up of effective interventions and are now moving toward malaria elimination. [2] In malaria control, the goal is to reduce the clinical burden of malaria. In malaria elimination, the aim is to interrupt transmission, and it becomes necessary to treat not only symptomatic malaria but also asymptomatic infections that perpetuate transmission. Malaria transmission is geographically heterogeneous, thus elimination activities should target hot spots, or areas where the risk of future infection is highest. Hence, in the transition from control to elimination, enhanced surveillance and response is necessary to target hot spots with interventions to interrupt transmission. [3, 4]

1.3 Reactive case detection (RACD)

For elimination, active surveillance in the communities around passively detected index cases, reactive surveillance or reactive case detection, is recommended as a strategy to identify secondary cases and hot

spots.[2-4]However, re-active surveillance can be low yield, labor-intensive, and costly.[4] Microscopy is being replaced by antigen-based rapid diagnostic tests (RDTs) that provide convenience but have limitations in the sensitivity to detect low parasite density and non-falciparum infections.[5, 6] PCR offers markedly improved sensitivity, but it requires hours of processing time, sophisticated technical skill, and expensive equipment to perform. Loop mediated isothermal amplification (LAMP) offers the sensitivity of PCR and is easier to perform but the requirement that samples be performed in a laboratory limit its usefulness for population level screening and treatment.

Household members and neighbors around index cases harbor infection

In Swaziland, reactive case detection involves the screening of household members and neighbors residing within 500 meters of the index case. Preliminary data from reactive case detection in Swaziland show that reactive case detection is a useful strategy to find asymptomatic infections and hot spots. From September 2012 to April 2014, 74 additional infections were identified by LAMP in households and neighbors of 263 index cases, resulting in a 28% increase in the detection of infections. Residence near the index case was associated with a higher risk of infection. Residing within 100 meters of index case was associated with a 4.6 higher odds (95% CI 2.0 to 10.6) of infection compared to a baseline OR of 1.0 at 201-500m. Travel outside Swaziland and Mozambican nationality were associated with infection. However, excluding these individuals resulted in a similar finding: residing within 100 meters of index case was associated with a 4.2 higher odds (95% CI 1.7 to 10.4) of infection compared to a baseline OR of 1.0 at 201-500m (Figure 3).

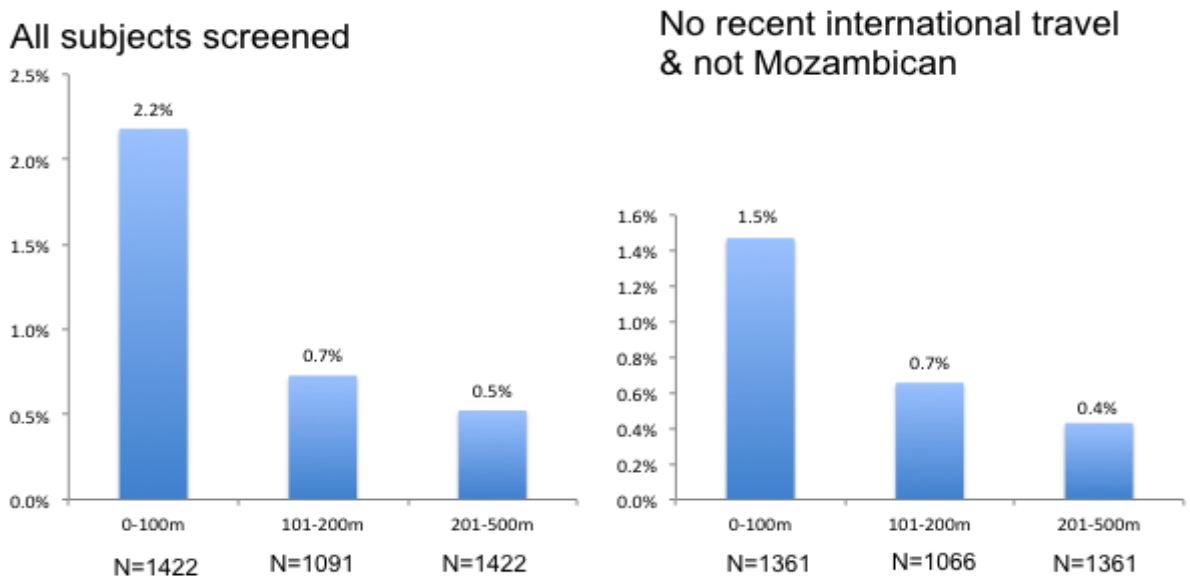

Figure 3. LAMP positivity by distance from index case

Challenges with reactive case detection

There have been challenges with reactive case detection. Firstly, achieving high coverage is challenging. At present, coverage is about 60% of the individuals residing in the Target Area. Working individuals and school children are often not available when the study team visits, and some, albeit few, do refuse to give blood. Of those reached, the work is low yield. Of 8355 people screened from September 2012 to May 2014, there have only been 42 (0.5%) RDT positives. Further, the sensitivity of RDT is poor for detecting low-density infections in asymptomatic individuals. The sensitivity of RDT compared to PCR as gold standard to detect these asymptomatic infection is 20%. LAMP increases the detection of infection by 1.6 fold but the positive rate is still extremely low at 0.9%. Furthermore, due to the long turnaround time, it has been logistically challenging to treat in a timely fashion based on LAMP results.

Also, it is suspected that even LAMP using dried blood spots is missing infections. Others have reported prevalence of infection in low transmission areas to increase by 1.4 fold when performing PCR using a higher volume of whole blood (200uL) compared to using 5uL of blood, about the amount of blood available from a punch from a DBS (Canier and Menard, unpublished data from Cambodia). Using PCR, Imwong *et al.* showed sometimes 50x higher sensitivity using 1 mL of blood compared to DBS. [7] Interestingly, 11.4% of reactive case detection events resulted in the identification of at least one additional infection by RDT. 16.7% of reactive case detection events resulted in the identification of at least one additional infection by LAMP. The apparent discordance between neighborhood versus individual level positivity rates suggests that there might be more infections that are being missed by even LAMP. To collect higher volumes of blood in a focal screening and treatment setting would be impractical.

1.4 Targeted parasite elimination (TPE)

Given the limitations in a reactive case detection approach to identifying low-density infections, as well as the logistical challenges and cost associated with the screening process, presumptive treatment may be a more effective for reducing and interrupting transmission and more feasible to implement. Treatment may also have a prophylactic effect, particularly if the drug has a long half-life such as dihydroartemisinin-piperaquine (DP).

TPE is a form of mass drug administration (MDA); some have called it focal or targeted MDA. Instead of targeting large populations, TPE is directed at the highest risk individuals. In China, an "outbreak" or reactive TPE strategy that targets the household members and neighbors of index cases detected through passive surveillance has been shown to have likely contributed to interruption of transmission [8]. Previously when transmission was higher, entire counties were targeted. However, as transmission declined, local officials found that there was increased resistance to take drugs. Household members and neighbors of index cases perceived a higher risk of malaria and were more likely to take drugs. Using this strategy, only about 20-50 individuals are targeted. Modeling suggests that coverage rates of at least 80% are needed for MDA to be effective, and targeting a smaller population size helps to maximize acceptance and adherence.

When TPE should be implemented is not known and likely needs to be tailored to the local epidemiology. For example, in areas where there is a known reservoir of infection, using a proactive approach, e.g. before the transmission season, may help to eliminate the local reservoir to prevent onward transmission. However, in an area such as Swaziland, where a larger proportion of infections are imported and these may be seeding local transmission, a reactive or outbreak approach may be more effective and operationally feasible.

1.5 RACD vs. reactive TPE

TPE is a promising strategy, but evidence does not yet exist to prove its effectiveness in Africa.[1] There are also questions about the feasibility in terms of coverage, safety, acceptability to the community, and cost-effectiveness. 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	+ does not rely on insensitive diagnostics + may provide prophylactic effect
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 drug (without testing) may facilitate high coverage at first encounter, but logistics to complete 3 day course of drug but be challenging
	Acceptability	+/- acceptability high but occasional refusals due to community dislike for giving blood	+/- anticipate some refusals to take drug, but acceptability may be high (e.g. sensitization from deworming campaigns)
	Safety using ACT	+treatment of only test positive individuals is safe	?treatment of many asymptomatic individuals is likely to be safe but not known
	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 and perceived risk of malaria is high
	Cost-effectiveness	+/- /? costs high but usually a reasonable expense for a low transmission setting where the intervention can be targeted, not know where there could be cost-savings	?relative cost-effectiveness to the standard of care (RACD) not known

1.6 Drug regimens

For an individual receiving TPE, the goal is to treat any existing reservoir of infection. Prevention of future infection, as possible given the half-life of the drug is an added bonus. In Swaziland, Artemether-lumefantrine (AL or Coartem) is the first line therapy for *Pf* infection. The drug is generally well tolerated with minimal adverse effects. Doses are weight adjusted for children and a pediatric dissolvable version is available. One challenge is that the drug requires frequent administration. The second dose is administered 8 hours after the first dose and then 1 dose is given twice daily for 2 more days. Also, due to lack of data, it is not indicated for children <5kg. Pregnancy during the first trimester is also a contraindication. Animal studies suggest that fetal absorption could lead to early pregnancy loss.

Dihydroartemisinin-piperaquine (DP) is another safe and efficacious ACT regimen recommended by the WHO, and now recommended as a second line therapy for uncomplicated malaria in many countries. A recent Cochrane review of DP included 27 trials conducted between 2002 and 2010, enrolling 16,382 adults and children[9]. Most trials excluded infants aged less than six months or <5 kg as well as women who were pregnant or breastfeeding. In Africa, over 28 days, DP was superior to AL in that there was less treatment failure (PCR-unadjusted treatment failure: RR 0.34, 95% CI 0.30 to 0.39, nine trials, 6200 participants, high quality evidence). Although PCR-adjusted treatment failure was below 5% for both ACTs, it was consistently lower with DP (PCR-adjusted treatment failure: RR 0.42, 95% CI 0.29 to 0.62, nine trials, 5417 participants, high quality evidence). DP has a longer 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 a previous review of DP, an association was noted between DP and prolongation of the QT interval in two small observational trials. Prolonged QT interval is a cardiac conduction defect that can sometimes lead to fatal arrhythmias[10]. However, in the same Cochrane review, compared to AL, no difference was seen in prolonged QTc, and no cardiac arrhythmias were reported. The frequency of other adverse events is probably similar with both combinations.

A Ugandan study of regimens available for intermittent preventative therapy (IPT) - an MDA strategy used in high transmission settings - identified DP as the most effective and best-tolerated regimen among school children [11]. Studies of DP in Uganda, including trials of very young children,[12, 13] children under ten,[14, 15] and school-aged children,[11] have found no increase in safety risk associated with DP consistent with other studies. Additional benefits of DP are that it can be administered just once daily and the long half-life of the partner drug piperaquine provides a protection again subsequent infection. Given these characteristics, DP has been suggested as an optimal candidate for community based MDA.[16]

ACTs treat early gametocytes, the parasite stage responsible for subsequent transmission, but they do not treat mature gametocytes. The use of single dose primaquine in addition to ACT has been proposed as a strategy to help interrupt malaria transmission and it is currently recommend by WHO for symptomatic cases. However, no there are no guidelines for use in asymptomatics. The potential risk is hemolysis in individuals with underlying G6PD-deficiency. The unavailability of a simple and inexpensive rapid test for G6PD deficiency complicates the use of primaquine. Recent modeling suggests limited added benefit of primaquine to ACT alone in MDA. In an individual with asymptomatic parasitemia, ACT alone is likely to decrease the period of gametocytemia from months to about 2-6 weeks. The addition of primaquine will decrease that period to about one week. The slightly prolonged period of gametocytemia may not be relevant in a low transmission setting, particularly considering the potential risks.

It has been proposed that MDA be administered by directly observed therapy of DOT, the rationale being that high coverage is critical to the success of MDA. Individuals who are not ill may be less adherent with medication, though adherence may be high when the perceived risk of infection is high such as in this study where a family member or neighbor will have recently been diagnosed with malaria. In a review of the published MDA literature, 12 successful studies reported the method of drug delivery and six utilized DOT or modified DOT. Drug distribution and observation was performed by community volunteers, local health workers, study authors and/or external organizations. [17] While strict DOT would ensure the highest adherence, it may not be practical for under-resourced malaria programs, particularly during the high transmission season when malaria staff are busy. Also, many individuals may be away at school or work during the day, making strict DOT challenging. In order to evaluate a strategy that can be feasibly implemented by malaria programs, drugs will be delivered using a modified DOT strategy.

2 Rationale

Overall Rationale

Current work in RACD suggests that it is useful in the identification of asymptomatic infections and hotspots, but there are some logistical challenges such as specimen collection, laboratory testing, and the need for return visits to treat asymptomatic individuals that were initially missed by RDT or microcopy but subsequently positive by molecular testing. Even with use of a molecular test such as LAMP that has a relatively fast turnaround time, subjects can be lost to follow-up. In addition, even molecular detection methods that are more sensitive than RDT or microscopy, they may still be missing very low parasite density infections. TPE has potential to be more feasible to implement and potentially more effective.

Current strategies in Swaziland may not be sufficient to achieve elimination. In the past year, the number of locally acquired cases has increased relative to the two prior years (Figure 2). In order to achieve elimination in Swaziland, there is an urgency to pilot and evaluate new strategies. These findings will not only benefit Swaziland but also other eliminating countries.

Rationale for the study design and selected study outcomes

In this study, we will utilize a cluster randomized controlled study design to evaluate TPE and compare it to RACD in response to a passive identified index case. As both locally acquired and imported infections contribute to Swaziland's overall malaria burden and can cause onward transmission, individuals who

acquired their *Plasmodium* infections within their community and abroad will both be included as index cases triggering a response.

Effectiveness to interrupt transmission is an obvious outcome of interest for this study. Entomologic inoculation rate (EIR) is the gold standard measure of transmission; however, given the extremely low sporozoite rates among mosquitoes in low transmission settings such as Swaziland, this is an impractical measure for this study. Instead, for *our primary outcome,* we will measure the locality or cluster-level cumulative incidence of malaria cases over two transmission seasons. As secondary outcomes measures of effectiveness, we will also measure proportion of imported incident cases, as well as the time to first subsequent incident local case post-intervention. While incidence is a standard measure captured through health facility reports, it does not capture asymptomatic infections in the community. Therefore, we will also conduct a cross sectional survey toward the end of the study (estimated mid 2017) at the end of the transmission season to measure seroprevalence and prevalence. Finally, we will measure transmission potential as measured by relatedness of detected infections (from passive surveillance or the follow-up survey) using genotyping. These additional measures of transmission were not selected as primary outcome measures for several reasons. Seroprevalence and genotyping are exciting but still investigational diagnostic methods. Post-intervention prevalence of asexual and sexual stages may be too low for comparison though we will optimize our chances of detecting infection by collected higher volumes of blood and focusing in the highest risk areas (Target Areas). Nonetheless, we will evaluate these measures of effectiveness and may be able to find that one arm is superior to another for a particular outcome measure. These findings will be useful for Swaziland and for higher endemic settings where it might be easier to evaluate impact.

For MDA to be effective, it has been proposed that at least 80% coverage of the target population is necessary[18]. A TPE experience from China - targeting household members and neighbors of index case, as in this study – also suggests that high, generally >85% coverage, is needed to interrupt transmission [8]. There is no evidence to show that high coverage of TPE is feasible. Some challenges for high coverage of TPE versus RACD include willingness to take drug without knowing infection status and time it takes for staff to explain rationale for taking drugs. 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. We will also compare coverage to that achieved in RACD arm but we will not be powered to detect superiority of either approach (RACD coverage is expected to be at least 80%), or non-inferiority of TPE given the high sample size that would be required.

Other key aspects of feasibility will also be evaluated, including safety, acceptability, costs, and adherence. The ideal study to evaluate safety would involve a placebo arm. As the primary aim of this study is not to evaluate safety, and because there is already robust evidence to suggest that AL and DP are safe, including in asymptomatic individuals (e.g. with IPT), we will not include a placebo in the study but we will record serious adverse events in both the RACD and TPE arms. Acceptability of TPE vs. RACD will be evaluated through a qualitative assessment (the Acceptability Assessment) and quantitative analysis of refusal rates. The costs and relative cost-effectiveness of TPE vs. RACD will be evaluated by a detailed costing exercise. In order to evaluate a strategy that can be feasibly implemented by malaria programs, drugs will be delivered using a modified DOT strategy. Ingestion of the first dose of drug will be directly observed, and then the two subsequent doses will be left with the subject to self-administer at the same time on the subsequent 2 days. During up to 2 return visits, study staff may: document reported intake, make reminders, or observe ingestion of the drug. Adherence to DP will be measured by performing a pill count amongst residents of Target areas surrounding the first index case detected in each transmission season in each locality in the TPE arm.

Finally, cluster randomized controlled trials are the gold standard to compare health services and policy interventions, but significant inputs in time and resources are usually required rendering this study design impractical in program settings. However, as we propose in this project, when many cases are easily available (index cases reported through passive surveillance), existing infrastructure is in place (the current

surveillance team), and the outcome measures can be feasibly measured (incidence will be collected through routine case reporting data, with secondary outcomes measures mainly collected through minimal follow-up visits), a cluster randomized controlled trial can be performed quickly and efficiently.

3 Study aims

The **overall objective** of this proposal is to critically evaluate TPE vs. RACD as a surveillance and response strategy for malaria elimination.

Our **primary aim** is to:

Compare the impact of TPE versus RACD on incidence of malaria cases. We will test the hypothesis that TPE compared to RACD will result in a lower cumulative incidence.

In addition, the following **secondary aims** will be addressed:

Effectiveness:

1. To compare the impact of TPE versus RACD on seroprevalence. We will test the hypothesis that TPE, compared to RACD, will result in lower exposure to malaria, as assessed by antibodies to antigenic markers of recent exposure near the end of the study period (expected mid 2017).
2. To compare the impact of TPE versus RACD on prevalence of infection. We will test the hypothesis that TPE, compared to RACD, will be more effective in decreasing the prevalence of infection near the end of the study period (expected mid 2017).
3. To compare the impact of TPE versus RACD on the proportion of imported incident cases. We will test the hypothesis that TPE compared to RACD will result in a higher proportion of imported incident cases.
4. To compare the impact of TPE versus RACD on time to first incident local case subsequent to the intervention. We will test the hypothesis that TPE compared to RACD will result in a longer time to the first incident local case.
5. To compare the impact of TPE versus RACD on transmission potential, measured by relatedness of strains by microsatellite genotyping. We will test the hypothesis strains detected in TPE versus RACD are less related to ancestor infections.

Feasibility:

1. To determine the feasibility of obtaining at least 80% coverage of TPE, and compare coverage to that attained using RACD. Coverage will be defined as receipt of and adherence to the first dose of DP within initial visits by the study team in the TPE arm or receipt of a blood test in the RACD arm. Our hypothesis is that the coverage attainable for TPE will be at least 80%. We also hypothesize that coverage for TPE will be equivalent to RACD but we will not be powered to prove this hypothesis.
2. To measure adherence to a 3-day regimen of DP administered by modified DOT delivery system in the TPE arm. We hypothesize adherence will be 80%.
3. To compare potential serious adverse events associated with TPE and RACD. We will test the hypothesis that the risk of serious adverse events will not be higher in individuals receiving TPE versus RACD.
4. To compare the acceptability of TPE versus RACD as assessed by refusal rates and a qualitative assessment. We hypothesize that TPE will not be inferior to RACD in terms of acceptability and may be more desired.
5. To compare the costs of TPE versus RACD. We will test the hypothesis that the costs per event will not be higher for individuals receiving TPE compared to RACD and may be cost-saving.

4 Study design & methods

4.1 Overview

We will evaluate the impact and feasibility of TPE versus RACD as a surveillance and response strategy in the communities around passively detected index cases using a cluster-randomized trial umbrella study design. To facilitate operations of the trial and subsequent roll-out of the TPE intervention should it be shown to be effective and feasible, the randomization will occur at the administrative level of the locality. A total of 77 historically at-risk study localities or clusters will be included in the trial; 39 will be randomized to the TPE intervention, and 38 to the control intervention (RACD) (Figure 4). If new malaria hotspots are detected during the study period, these additional localities may also be included in the study at the discretion of the study team, in consultation with the Swaziland National Malaria Control Programme. These additional study localities will be randomly assigned to receive either the RACD or the TPE intervention. Target areas for localities randomized to receive TPE will be defined as all individuals residing within 200m of an index case that is detected in passive surveillance and resides in a TPE locality, with individuals residing immediately beyond 200m included if a minimum of 30 individuals are not enrolled within 200m. Target areas for localities randomized to receive RACD will be defined as all individuals residing within 500m of an index case that is detected in passive surveillance and resides in a RACD locality (as per current policy in Swaziland), while focusing on maximizing coverage within the immediate 200m radius around the index case. Per current policy, for individuals receiving RACD, blood will be collected for RDT and DBS and subjects testing positive on RDT will be referred to a local clinic for treatment with AL. In the TPE arm, blood will not be collected and presumptive treatment will be administered by modified DOT. Incidence data will be collected passively during the study period. For secondary outcome measures, in select Target Areas, a pill count will be conducted 7-10 days after the first visit day and a qualitative Acceptability Assessment will be conducted with study participants at the time of the pill count. Passive monitoring for serious adverse events (SAEs) will occur in both the TPE and the RACD arms. To measure prevalence and seroprevalence, a cross sectional survey will be conducted in Target Areas near the end of the study (during the end-line survey, expected to take place mid 2017). Finally, to validate the serological markers, a follow-up survey will be conducted at 6-9 months among any individuals who were infected at baseline (index cases in both arms as well as secondary cases detected by RDT at baseline in the RACD arm).

4.2 Study site and study population

The control and test interventions for this study will take place in the eastern half of Swaziland where RACD is currently conducted and focus in 77 localities (or sub-districts) which contains 431 EA (enumeration areas) but only 139 historically at-risk EA (Figure 4). To recruit Target Areas, the study will utilize the existing health infrastructure throughout Swaziland. Laboratory confirmed index cases present through passive surveillance and are reported through a toll free “977 Hotline.” Health facilities are shown in Figure 5. Although all index cases are targeted for a follow-up case investigation (questionnaire with capture of GPS coordinates at the home of the index case), only index cases residing in the study localities will be enrolled in the study. Index cases not residing in study localities will not directly contribute to the study, but samples from these cases will also be genotyped (see section 12.7) to allow for more accurate classification of study subjects as having acquired their infection locally vs. being imported based on circulating parasite genotypes. Both locally acquired and imported cases can trigger the study intervention. The six catchment areas are covered by different surveillance agents with one officer covering Vuvulane and Ndzevane (Lubombo region) and another officer covering the other four catchment areas.

4.3 Randomization of localities (clusters)

The randomization will be conducted by a member of the study personnel who is not directly involved in the field activities. A block stratified randomization method will be used to randomize the localities by risk

rank as well as population within 139 historically at-risk EA. The local surveillance group has ranked localities into three groups by risk of incident malaria. Before the study is launched, additional at risk localities may be added if the area is confirmed to have had local cases in the past 3 years. The risk rank stratification will ensure equal distribution of higher and lower risk localities between the TPE and RACD arms. Randomization will take place before the study to facilitate sensitization of the community. All Target Areas within a randomized locality will follow the same intervention protocol. A list of the 77 randomised localities is shown in Table 2. The table also shows total population of the 431 EA in these 77 localities as well as the population in historically at-risk EAs (139 EA in 77 localities), and finally the expected at-risk population (105 EA in 63 localities with cases sept 2012-mar2015) used for sample size and power calculations (see section 14)..

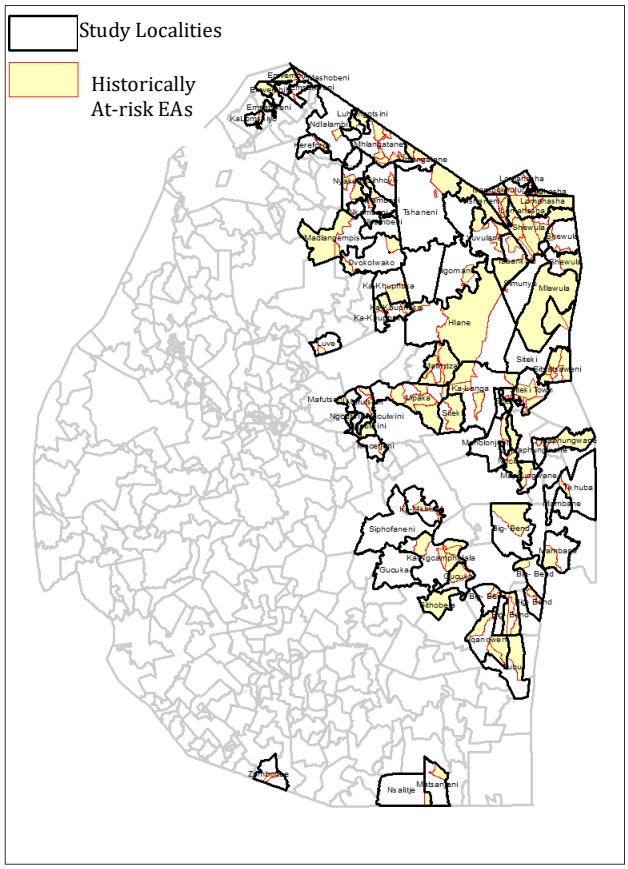

Figure 4. Study Localities outlined in black with historically at-risk enumeration areas (EA) shaded in yellow

Table 2. List of study localities with case reports over the last 3 years with risk rank and total population (431 EA in 77 localities) and expected at-risk population (based on 105 EA with cases sept 2012-march 2015)

				Data from Sept 2012-March 2015					
Locality Code	Unique Locality Name	Risk Rank	Local Cases	Imported Cases	Incident Cases (Local + Imported)	Secondary Cases	Total Population	Historically at-risk population	Expected at-risk population
139000	MANZINIMAFUTSENIMafutseniBhudla	1	0	0	0	0	3498	1245	0
365000	LUBOMBOTIKHUBATikhubaMatsenjwa	2	0	0	0	0	2293	545	0
421000	LUBOMBOLUGONGOLWENIMlawulaSiweni	3	0	0	0	0	176	176	0
188000	HHOHHONTFONJENIEmsahweniTimpisini	2	0	0	0	0	719	719	0
428000	LUBOMBOMHLUMENgomaneNgomane	2	0	0	0	0	2118	330	0
487000	LUBOMBODVOKODVWENIMacetjeniMphosi	3	0	0	0	0	2419	529	0
482000	LUBOMBONKILONGOBig-BendMndobandoba	3	0	0	0	0	2470	558	0
129000	MANZINIMAFUTSENINgculwiniNtabamhloshana	1	0	0	0	0	1609	637	0
378000	SHISELWENIZOMBODZEZombodzeMahlabathini	3	0	0	0	0	1947	344	0
195000	HHOHHOMAYIWANEHerefordsJacks	3	0	0	0	0	1954	492	0
140000	MANZINIMAFUTSENIMafutseniEkuchwaleni	1	0	0	0	0	1824	287	0
471000	LUBOMBONKILONGOSithobelaNkonjwa	3	0	0	0	0	50	50	0
180000	HHOHHOTIMPISINIEmvembiliMvembili	1	0	0	0	0	2534	436	0
419000	LUBOMBOMHLUMESimunyeLusoti	3	0	0	0	0	4014	576	0
426000	LUBOMBOMHLUMETshaneniVuvulane	3	1	0	1	0	279	279	279
350000	LUBOMBOLUGONGOLWENISitekiMhlumeni	3	1	0	1	0	547	503	454
438000	LUBOMBOLOMAHASHALomahashaNgulubeni	1	1	0	1	0	894	394	394
425000	LUBOMBOMHLUMETshaneniTshaneni	3	0	1	1	0	2366	962	441
439000	LUBOMBOLOMAHASHALomahashaMatfuntini	1	1	0	1	0	1404	677	677
367000	LUBOMBOMPOLONJENIMaphungwaneMagwanyana	1	1	0	1	0	1779	767	767
480000	LUBOMBONKILONGOBig- BendMayaluka	3	1	0	1	0	2305	353	353
366000	LUBOMBOTIKHUBAMambaneMambane	2	1	0	1	0	4179	686	686
406000	LUBOMBOMPOLONJENIMpholonjeniLokhayiza	2	1	0	1	1	5561	592	592
412000	LUBOMBOMPOLONJENINgcinaNyetane	1	1	0	1	0	612	612	593
209000	HHOHHOMHLANGATANENkambeniMabiya	2	1	0	1	0	541	541	541
211000	HHOHHOMHLANGATANESihhoyeMbangave	2	1	0	1	1	3722	550	550
351000	LUBOMBOMPOLONJENIMaphungwaneSigwenyameni	2	0	1	1	0	2037	494	494
383000	SHISELWENIMATSANJENIMatsanjeniMabande	2	0	1	1	0	3410	762	762
381000	SHISELWENIMATSANJENINsalitjeSitilo	2	1	0	1	0	1901	607	607
128000	MANZINIMAFUTSENINgculwiniThulwane	1	1	0	1	0	1789	630	630
147000	HHOHHOMHLANGATANENkambeniNkambeni	2	1	0	1	0	1604	399	399
359000	LUBOMBOLUBULILubuliNsoko	2	0	1	1	0	2636	501	501

362000	LUBOMBONKILONGOBig-BendMahlabaneni	3	1	0	1	2	1493	831	224
255000	HHOHHOMAYIWANENdlalambiMbasheni	3	0	1	1	1	9079	518	518
203000	HHOHHONTFONJENIKaLomshiyoLomshiyo	3	1	0	1	2	1901	368	368
120000	MANZINIMKHIWENILuveMfangibhekile	3	1	0	1	0	2911	532	532
116000	MANZINIMKHIWENIKa-KhuphukaMliba	1	1	0	1	0	1885	900	900
484000	LUBOMBOSIPHOFANENISiphofaneniMadlenya	1	2	0	2	0	7166	891	891
475000	LUBOMBOSITHOBELAGucukaMalayinini	1	2	0	2	0	5292	972	972
183000	HHOHHOTIMPISINIMashobeniMashobeni	3	2	0	2	1	1402	485	485
346000	LUBOMBODVOKODVWENISitekiSiteki	3	1	1	2	2	4031	1369	805
441000	LUBOMBOLOMAHASHATsambokhuluMacakula	3	2	0	2	0	1210	826	445
347000	LUBOMBOMPOLONJENISitekiSiteki	1	0	2	2	1	500	500	500
464000	LUBOMBOLOMAHASHAMambaneLucaceni	1	2	0	2	1	868	485	485
114000	MANZINIMKHIWENIKa-KhuphukaMnjoli	1	2	0	2	0	1053	504	504
148000	HHOHHOMADLANGAMPISINkambeniNkambeni	2	3	0	3	1	1841	509	509
416000	LUBOMBOLOMAHASHAShewulaShewula	2	1	2	3	0	4578	1349	921
403000	LUBOMBOSIPHOFANENIKa-MkhweliKa-Mkhweli	2	3	0	3	1	5488	1394	1394
146000	HHOHHOMHLANGATANEMhlangataneNhlanguyavuka	1	2	2	4	1	3654	1060	1060
182000	HHOHHOTIMPISINIEmvembiliNkonjaneni	1	4	0	4	2	470	470	470
189000	HHOHHOTIMPISINIEmsahweniTimpisini	2	4	0	4	0	2467	601	601
256000	HHOHHOMHLANGATANELuhlangotsiniLuhlangotsini	2	4	0	4	0	1215	819	819
418000	LUBOMBOMHLUMETabankuluTabankulu	1	3	1	4	1	1498	562	562
437000	LUBOMBOLOMAHASHALomahashaMafucula	3	4	0	4	0	1607	741	741
363000	LUBOMBONKILONGOBig- BendMatata	3	2	3	5	0	903	726	726
417000	LUBOMBOLOMAHASHAShewulaNhlungwini	3	0	5	5	1	1145	692	692
212000	HHOHHOMADLANGAMPISIMadlangempisiMandlangempisi	2	4	1	5	1	4550	1093	1093
423000	LUBOMBOHLANEHlaneHlane	3	4	1	5	1	3326	844	844
435000	LUBOMBODVOKODVWENIMpakaMpaka	2	3	2	5	0	6885	3260	1333
463000	HHOHHOMADLANGAMPISIDvokolwakoManzana	1	5	0	5	0	6047	1094	1094
207000	HHOHHOMHLANGATANENyakatfoZwayimbane	2	2	3	5	0	4964	1227	1227
407000	LUBOMBODVOKODVWENIKa-LangaLukhula	3	2	4	6	2	9015	2123	926
452000	LUBOMBOLUBULINqandweniSicelwini	2	3	3	6	3	3557	1536	1536
345000	LUBOMBOLUGONGOLWENISitsatsaweniBhandeni	1	7	0	7	2	2363	1796	1271
427000	LUBOMBOMHLUMEVuvulaneVuvulane	1	6	1	7	3	2853	1765	1765
115000	MANZINIMKHIWENIKa-KhuphukaKa-Bheni	1	8	0	8	2	2755	1408	1408
432000	LUBOMBODVOKODVWENIMalindzaSikhuphe	2	6	2	8	1	3526	2920	2293
404000	LUBOMBODVOKODVWENISitekiKhushweni	2	5	4	9	5	1773	799	799
349000	LUBOMBOTIKHUBAMaphungwaneMhlaboubovu	1	9	1	10	5	2172	1115	542
150000	HHOHHOMHLANGATANEMhlangataneZinyane	1	12	2	14	6	5869	2328	1745
179000	HHOHHONTFONJENIEmvembiliMvembili	1	13	1	14	4	1456	689	689
440000	LUBOMBOLOMAHASHALomahashaLomahasha	1	5	10	15	4	2485	1960	1573

420000	LUBOMBOLOMAHASHAShewulaNduma	1	13	4	17	7	3894	3043	3043
481000	LUBOMBONKILONGOBig- BendVillages, Ka-Goboyane	1	2	15	17	14	890	418	418
415000	LUBOMBOLUGONGOLWENISiteki TownSiteki Town	2	9	13	22	6	4796	2377	2377
436000	LUBOMBOLOMAHASHALomahashaNkalashane	1	22	3	25	3	4154	2307	1886
473000	LUBOMBOSITHOBELAKa-NgcamphalalaMahlabatsini	1	35	6	41	20	5011	2222	2222
	Totals:	236	97	333	108	211189	71661	55928	

Unique Locality Name generated using names of Region, Constituency, Name1 and Name2 from Shapefiles.
Risk ranks 1 to 3 (highest risk being risk rank 1) assigned by NMCP according to historical and recent transmission.
Secondary case data based on LAMP data from reactive case detection, shown but not used for randomization as trigger for the study intervention, and primary outcome measure for the study is only based on incident cases.
Total population data from 2007 census data.
Historically at-risk population calculated as population of enumerations areas with recent and historical transmission.
Expected at-risk population calculated as population of enumerations areas with recent cases (sept 2012-mar2015).

4.4 Target Areas

The Target Area will be defined for TPE localities as all individuals residing within 200m of an index case that is detected in passive surveillance and resides in a TPE study locality, with individuals residing immediately beyond 200m included if a minimum of 30 individuals are not enrolled within 200m. This Target Area size was selected based on the existing RACD data whereby the mean number of individuals screened per index case was 32.

The Target Area will be defined for RACD localities as all individuals residing within 500m of an index case that is detected in passive surveillance and resides in a RACD locality. The malaria surveillance team will be trained to focus on maximizing coverage within the immediate 200m radius around the index case. This Target Area size was selected based on the current RACD policy in Swaziland.

Based on collected data on missing individuals, the estimated total number of individuals residing within 200m of an index case is 53. Thus, coverage to date for RACD has been 60%. However return visits do not typically occur at off hours (mornings and evenings). Moving forward, at least one return visit must occur during off-hours to ensure better capture and to maximize the sample size.

If a subsequent index case is reported in a target area (identified either through health facilities or RACD (all secondary cases identified in RACD become index cases)), the RACD intervention will not be repeated within 5 weeks (per current national policy). For the TPE arm, the intervention will not be repeated within 8 weeks or more than twice within the past year (DP drug insert recommends no repeat course within 8 weeks, and no more than 2 courses within one year).

Target Areas that reside on the border between two localities that were randomized to different arms will receive the intervention according to the locality randomization of the index case. For outcome measures, some contamination of the intervention arm's effect may occur if a neighboring locality is randomized to a different intervention. In the analysis we will adjust for distance from an index case for whom the surrounding area received TPE intervention. It will not be necessary to adjust for distance from an area where RACD was conducted because RACD is the current standard of care in all receptive areas of the country.

Based on past surveillance data, we expect about 134 index cases per study year. To demonstrate the seasonal pattern, Figure 6 shows the number of RACD events by month from 2012 to 2014. Due to capacity

limitations, not all eligible index cases received RACD. However after more staff were hired, almost all eligible index cases received RACD.

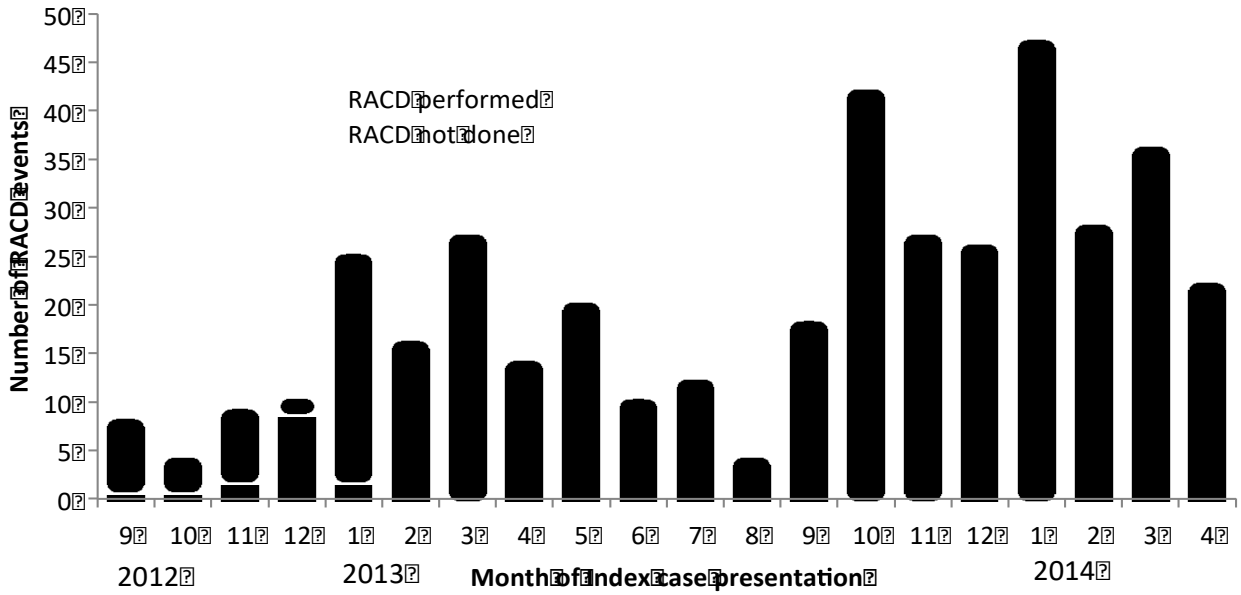

Figure 6. RACD events by month

4.5 Inclusion and exclusion criteria

Table 3. Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Index case (as trigger for RACD or TPE in their household members and neighbors)	• Malaria infection (either locally transmitted or imported) detected at a health facility through passive surveillance, and • Resided in a study locality.	• Malaria infection identified through screening.
RACD intervention	• Non-index case, and • Resided or spent at least one night in the Target Area in the past 5 weeks.	• Target Area overlaps with prior Target Area that received the RACD intervention within the past 5 weeks.
TPE intervention	• Non-index case, and • Resided or spent at least one night in the Target Area in the past 5 weeks.	• Target Area overlaps with prior Target Area that received the TPE intervention within the past 8 weeks, and • For DP specifically (though still eligible for interview): — Temperature $\geq$ 38.0^{o}C, report of fever in the past 48 hours, or other illness (will be referred to the nearest health facility for further evaluation) — Pregnancy, breastfeeding, and women who have had menarche but no menses in the past 4 weeks — Children <9 months of age or <7 kg — Known allergy or history of adverse reaction to DP — Already taken 2 courses of DP in the past year or taken 1 course within the past 2 months — Moderate or severe renal or hepatic insufficiency — Currently with severe malaria — Family history of sudden death or of congenital prolongation of the QTc interval. — Known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval. — History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia. Any predisposing cardiac conditions for arrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction. — Electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia (including vomiting in child) — Recent treatment with medicinal products known to prolong the QTc interval that may still be circulating at the time that DP is commenced (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial agents)
Pill count	• Resides in the first Target Area to receive the intervention for each locality during each transmission season, and • Received antimalarial drugs through the TPE intervention.	• Resides in a locality randomized to the RACD arm.
Acceptability Assessment	• Received the TPE intervention, or • Member of surveillance team in both RACD and TPE arms.	• < 18 years of age.

6-9 month Follow-up visit	• Index case residing in either RACD or TPE study locality, or • Secondary case (RDT or LAMP positive at the RACD intervention), or • Non-infected control (RDT and LAMP negative at the RACD intervention).	• Non-index resident of a locality randomized to the TPE arm.
End-line survey (end of study)	• All individuals who resided or spent at least one night in the Target Area in the past 5 weeks (includes index cases and individuals who did not receive a study intervention).	• None.

NOTE: Medicinal products that are known to prolong the QTc interval include:

- *Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).*
- *Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine), antidepressive agents.*
- *Certain antimicrobial agents, including agents of the following classes: - macrolides (e.g. erythromycin, clarithromycin), - fluoroquinolones (e.g. moxifloxacin, sparfloxacin), - imidazole and triazole antifungal agents, - and also pentamidine and saquinavir.*
- *Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine).*
- *Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide*

5 Baseline Preventative Interventions – LLINs and IRS

Individuals residing in endemic areas will receive or will have received LLINs and IRS per standard procedures by NCMP. IRS is conducted once yearly before the transmission season, usually beginning in August and running through to February To maximize benefit of IRS to study participants, study staff with work with the vector control program to ensure high coverage of all target communities. During visits by spray teams, households will be sprayed if people are home. If not, return visits will be conducted to ensure a high coverage of IRS. LLINs will be provided to households that do not already have functioning insecticide treated bednets. We will monitor coverage of ITNs and IRS as well as timeliness of IRS.

6 Enrollment

6.1 Sensitization

Prior to starting the study, we plan to build awareness, secure commitment, and encourage participation from stakeholders at the national, regional, and local level. We will meet with members of the Ministry of Health, NMCP, Swaziland Laboratory Health Services, Swaziland Malaria Elimination Advisory Group for both Case Management and Surveillance, the Regional Health Management Teams from the receptive regions, local chiefdoms through Regional Administrators, and other appropriate officials in the health sector. Once approval has been granted by the appropriate officials, we will sensitize health facility workers and rural health motivators with an information sheet (Appendix A).We will also work with the health promotion and surveillance teams in sensitizing the community members in the localities selected for TPE.

The Target Areas for this study (whether randomized to TPE or RACD) will be identified as they have been for the current RACD program, therefore, there will be little time for sensitization prior to the visit by the study team. With the current RACD program, the index case is contacted by telephone before the visit and asked to notify other members of the household about the upcoming visit. Although neighboring households are not notified, refusals are rare. The overall high acceptance is thought to be due to perceived risk of malaria when it is known that a household member or neighbor had malaria. This perceived risk may facilitate acceptance of TPE. Indeed during RACD, community members have sometimes requested drugs when they do not want to give blood for screening. Also, Swaziland provides free malaria prophylaxis to individuals travelling to Mozambique. It is possible that familiarity with this strategy will also help facilitate acceptability of TPE. To further facilitate acceptability we will utilize rural health motivators. The study team will contact the rural health motivator prior to the visit and ask him or her to notify all eligible participants about the project. Rural health motivators will have already been sensitized about the

project (Appendix A). This pre-visit notification to all community members in the Target Area by the rural health motivator will also help improve coverage.

6.2 Identification of Target Areas (through immediate case notification and Case investigation of the index case)

Study participants will be recruited starting with index cases that are identified through a Case report/Case investigation system. After a laboratory confirmed index case is identified at a health facility, the health worker completes an Immediate Notification Form investigation (Appendix B) and reports the case through the country's toll-free Immediate Disease Notification System (977). The NMCP Surveillance Team is notified by an SMS text. A Surveillance Agent visit the health facility to collect the DBS, RDT, and slide, and visits the home of the index case within 48 hours and to administer a questionnaire and capture GPS coordinates, as part of the case investigation (Appendix C). Also, if a DBS was not collected by the health facility at the time of presentation, the surveillance agent also collects a DBS.

If the index case resides in a study locality, that neighborhood or Target Area will become enrolled in the study. During intervention resident enrollment, the study staff will begin recruiting study participants from the home of the index case, and then move on to neighboring households. On the first visit, the team will map the location of the index case and visualize the 200 or 500 meter radius on google maps while in the field. The team will attempt to enroll all individuals residing within 200 or 500 meters, depending on whether that Target Area has been randomized to receive TPE or RACE. On the second visit, the team must come at a time during which persons previously absent will be present (usually morning or late afternoon/early evening) and re-visit all households in which 100% coverage was not achieved. If 100% coverage is obtained, that Target Area intervention is complete. If not, on the 3rd visit, the team must also come at a time during which persons previously absent will be present (usually morning or late afternoon/early evening) and the study team must re-visit households in which 100% coverage was not achieved. If during this 3rd visit 30 individuals are not yet enrolled (participated in study intervention), the team will move onto the next closest house (but not beyond 500m) to screen individuals until at least 30 individuals are enrolled (but completing the screening in all individuals in that last household).

6.3 Informed consent

Informed consent will not be obtained from index cases for the Case Investigation as such procedures are part of standard surveillance in Swaziland. Informed consent will also be obtained from the household members and neighbors of the index case during the intervention resident enrollment visit. Informed consent will be obtained at all follow-up visits (the 6-9 month follow-up visit to collect blood for serologic testing and the end-line survey visit near the end of the study, expected mid 2017) for that day's study activities. Additionally, for the qualitative Acceptability Assessment (which will take place during the follow up pill count visit or 7-10 days after the intervention), informed consents will be obtained from selected residents at least 18 years of age in TPE Target Areas. Additionally, informed consent will be obtained from members of the surveillance team in both RACD and TPE arms for focus group discussions at 3 months intervals for the duration of the study.

Consents will be conducted in the participant's house prior to study activities. Consents will 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 children at once. Separate consent forms will be signed by each additional adult member of the house. Also, separate assent forms will be signed by each minor (12-17yrs).Informed consent will be conducted in the local language, SiSwati, or English, and a translator will be used if necessary (e.g. for Portuguese, though most Mozambicans are able to speak SiSwati). Consent forms will be available in English and SiSwati. As part of the informed consent process, study personnel will assess the participants understanding of the study procedures that were explained by the study staff using a checklist comprised of key components of the study. Subjects scoring at least 80% on the checklist will be asked to sign the written consent form. If the subject scores less than 80%, the consent discussion will be repeated, before asking for a signature. The consent form will be read again, focusing on areas where understanding was limited, and encouraging the subject to ask questions. If the subject is unable to read or write, their

fingerprint will substitute for a signature. If an interpreter is used, their signature will also be obtained. The informed consents that will be conducted and the study activities they cover are listed in Table 4.

For individuals <18 years of age, informed consent will be obtained from one parent or guardian, as is customary in Swaziland. Assent for adolescents 12-17 years of age will be obtained, as is customary in Swaziland.

Table 4. Informed Consents

<table>
<tr><th>Subject/Activity</th><th colspan="2">Informed consent covers</th></tr>
<tr><td>Index case</td><td colspan="2">• No informed consent as case investigation (questionnaire and DBS collection for malaria testing) is part of standard surveillance.</td></tr>
<tr><td rowspan="2">Resident Enrollment, Intervention (Appendices E, F)
• All residents of Target Areas</td><td>RACD</td><td>TPE</td></tr>
<tr><td>• At enrollment:
• Brief questionnaire and GPS mapping.
• Intervention blood testing with RDT & referral to health facility if RDT positive.
• Storage of blood with DBS, and with microtainer collection in RDT positives.</td><td>• At enrollment:
• Brief questionnaire and GPS mapping.
• If eligible for DP, 3 day course of DP by modified DOT.
• If not eligible for DP, blood testing by RDT & referral to health facility if RDT positive. Storage of blood with DBS, and with microtainer collection in RDT positives.
• 7-10 days post intervention:
• Potential pill count.</td></tr>
<tr><td>6-9 month Follow-up (Appendix L)
• All Index cases residing in Target Areas.
• All secondary cases and some RDT-negative controls from RACD localities.</td><td colspan="2">• At 6-9 months after diagnosis (Note: The study team will seek consent to collect a 6-9 month sample from index cases and RDT-positive residents who were diagnosed within in the 9 months prior to study launch):
• Follow-up blood testing with RDT & referral to health facility if RDT positive.
• Storage of blood with microtainer and DBS.</td></tr>
<tr><td>End-line survey (Appendix N)
• All residents of Target Areas.</td><td colspan="2">• At end-line survey, end of study:
• Brief questionnaire and GPS mapping.
• Follow-up blood testing by RDT & referral to health facility if RDT positive.
• Storage of blood with DBS.
• Brief interview.</td></tr>
<tr><td>Acceptability Assessment (Appendix U)
• TPE Study participants selected for inclusion in the Acceptability Assessment
• Surveillance team members in both RACD & TPE arms</td><td colspan="2">• TPE Participants: qualitative focus group discussions 7-10 days after intervention at pill count visits.
• Surveillance team: focus group discussions every 3 months for duration of study.</td></tr>
</table>

7 Study intervention

A schematic of the study interventions is shown in Figure 7.

7.1 Household-level questionnaire

A household will be defined as any single permanent or semi-permanent dwelling structure acting as the primary residence for a person or group of people that 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. A household resident will be defined as any person who has spent at least one night in the household in the past 5 weeks.

For each household enrolled in the study, a brief questionnaire will be conducted with the acting household head. The purpose of this questionnaire will be to determine household size and obtain information about the household structure as well as coverage of vector control interventions. If certain individuals are not present, the questionnaire will also aim to schedule a more suitable time to reach absent individuals. Separate questionnaires will be used for the RACD and TPE arms. The RACD household level questionnaire will collect blood testing results. The TPE questionnaire will collect information about doses of drugs administered (Appendix K).

7.2 RACD arm - Perform RDT and refer secondary cases to health facilities

Individuals residing in RACD clusters will be tested by RDT using the *Pf*-specific First Response RDT during the intervention visit. At the time that blood is collected for RDT testing, the same finger prick will be used to generate a slide and dried blood spot. Four spots of blood will be collected for each DBS. Subjects testing positive by RDT will be referred to the closest health facility for treatment according to national policy (first line AL, second line Oral quinine for uncomplicated malaria).

Secondary cases detected by RDT will become index cases (using the same unique study ID) and receive a case investigation. For these secondary cases, a second finger prick will also be performed to collect 250uL blood in a microtainer. These secondary cases will also be invited to participate in the 6-9 months follow-up as well as the end-line survey at the end of the study (expected mid 2017).

The microtainer samples collected from secondary cases will be used to develop serologic and genotyping methods. The rationale for a larger volume of blood is that serum is the gold standard sample for serologic assessment. Although DBS collection is more practical and has been validated for use in population level serologic assessments (as will be done at the end-line survey at the end of the study, expected mid 2017) [19], this microtainer sample will be used to develop and validate our serologic assay. A larger volume of blood draw will also facilitate genotyping. Secondary cases are mainly asymptomatic individuals with low-density infections. In our experience, microsatellites do not usually amplify well when using DBS in asymptomatics.

7.3 TPE arm - Administration of DP

Individuals enrolled in the TPE arm will be interviewed to determine if it is safe for them to receive DP (Eurartesim, Sigma Tau).

For individuals who can safely be given DP, the dose is one daily dose for 3 consecutive days. Participants will be weighed at enrollment, and DP will be dosed according to weight-based guidelines (Appendix Q). Half-strength DP tablets (20/160mg) or full strength DP tablets (40/320 mg) that have been cut into half will be given to children weighing $\leq$12kg, and full-strength tablets (40/320mg) will be given to those weighing >12kg.

The first DP dose will be administered by DOT. Subsequent doses will be left with the subject or guardian and subjects will be instructed to self-administer at the same time on Days 2 and 3. If a dose is missed, it should be taken as soon as realized and then the recommended regimen continued until the full course of treatment has been completed. No more than one dose on the same day should be taken to make up for any missed dose. Study staff will be revisiting neighborhoods for up to 2 additional days to enroll more subjects. On those days, the study staff may remind subjects.

The drug insert suggests that DP should be taken orally with water and without food, the concern being that food may increase absorption of piperaquine. However, there is limited data to support this practice. A trial by Lwin et al. in Thailand compared DP ingestion with or without chocolate milk and found both approaches to be safe, with no difference in drug levels or efficacy. [20] Several trials from Africa using DP in symptomatic as well as asymptomatic individuals have not required administration without food and have not found safety risks.[11-15, 21]. Given the limited data to show adverse events with food administration, and the practical challenges of administering DP without food in the field, we will not impose this restriction.

The shelf life of DP is 24 months. Expired drugs will not be used. As recommended, DP will not be stored above 30°C.

If an individual cannot safely be given DP, that individual will not be given medication for presumptive treatment. Pregnant women and breastfeeding women will be excluded. All girls ≥10 years of age will also be asked about menses. Those who have had menarche but have not menstruated in the past 4 weeks will also be excluded. Infants <9 months of age or <7 kg will also be excluded. For infants and children unable to take tablets, drugs will be crushed, mixed with water and administered as a suspension. No more than two courses of DP may be given within a 12-month period. Additionally, a second course of DP should not be given within 2 months after the first course due to the long elimination half-life of piperaquine. Other contraindications include: severe malaria, young children who vomit (electrolyte disturbances can increase QTc), heart problems or rhythm disturbances, kidney or hepatic insufficiency, recent treatment with certain medications (antiarrhythmics, neuroleptics, antibiotics, non-sedating antihistamines, antimalarial agents, and others (cisapride, droperidol, domperidone, bepridil, dephemanil, probucol, levomethadyl, methadone, vinca alkaloids, and arsenic trioxide).

Individuals who cannot safely be given DP will be tested by RDT using the *Pf*-specific First Response RDT during the intervention visit. At the time that blood is collected for RDT testing, the same finger prick will be used to generate a slide and dried blood spot. Four spots of blood will be collected for each DBS. A second finger prick will be used to collect microtainer blood samples from RDT-positive individuals. Subjects testing positive by RDT will be referred to the closest health facility for treatment with a drug that is safe for them according to national policy.

7.4 Management of sick participants

During the intervention, individuals who have a temperature of $\geq$ 38.0^{o}C, report having a fever in the past 48 hours, or have other illness will be referred to the nearest health facility for further evaluation.

7.5 Adherence assessment

In order to evaluate adherence to DP via modified DOT in the TPE arm, study staff may return in 7-10 days to perform a pill count. There is limited data on the expected adherence to the 3 day regimen among asymptomatic individuals. Among symptomatic individuals, the reported adherence ranges from 39 to 100%. [22] Due to the return visits by study staff, engagement of rural health motivators, and perceived risk among individuals residing near an index case, we hypothesize that adherence to a 3 day regimen will be 80%.

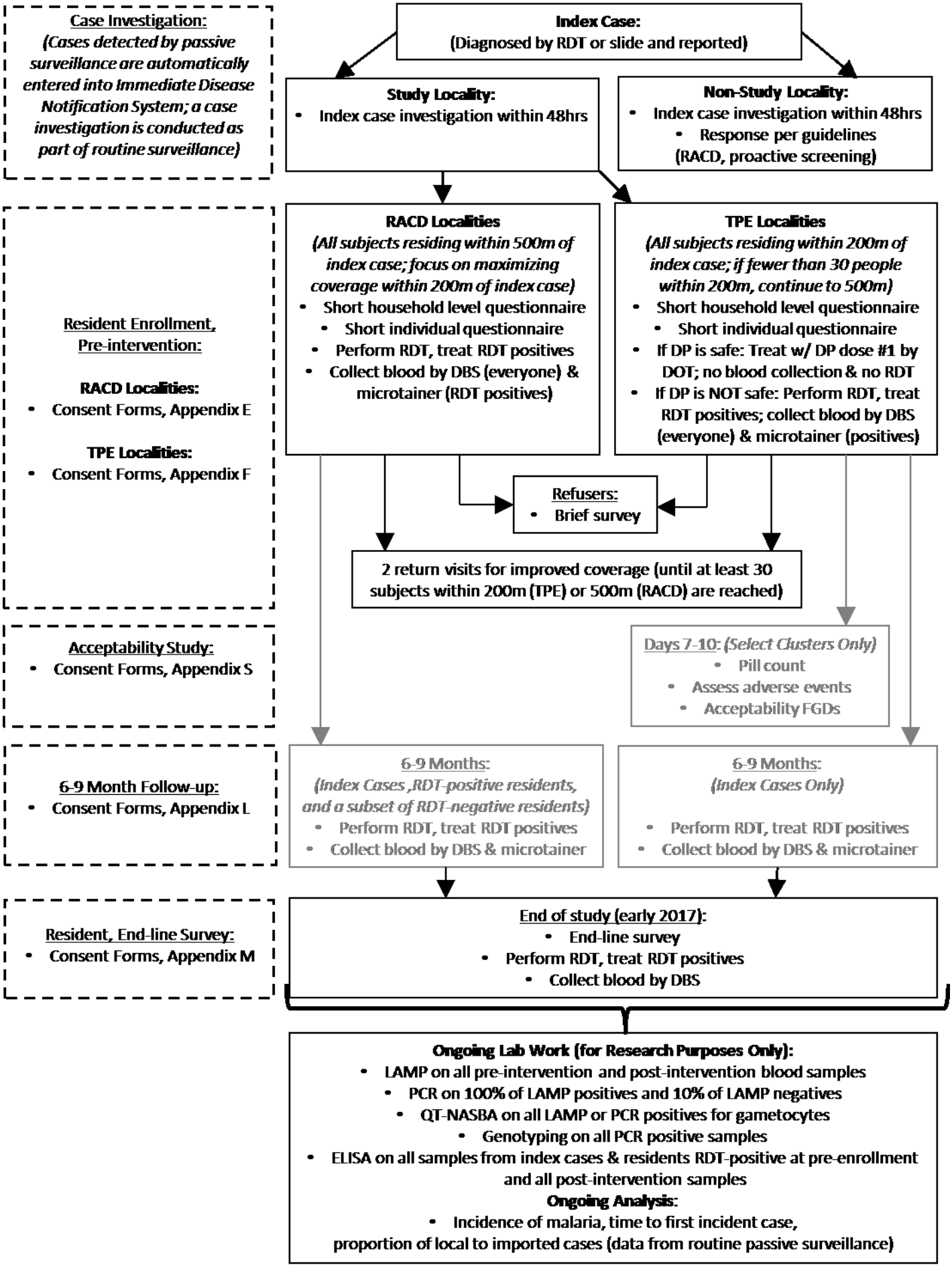

Figure 7. Study procedures.

8 Adverse event monitoring

8.1 Overview

The safety risks associated with participation in this trial are expected to be minimal. AL, the current standard of care in Swaziland, is generally well tolerated and, at least by passive monitoring, has been associated with only minimal adverse effects in Swaziland. DP is one of the ACT regimens recommended by the WHO[23], and is recommended as a second line treatment for uncomplicated malaria in many countries[24].The safety and tolerability of DP have been closely evaluated in clinical trials evaluating DP for treatment and prevention of malaria, and DP has been shown to have an excellent safety profile[10, 11, 25, 26]. In the TPE arm, prior to drug administration, subjects will be asked about known allergy, past adverse reactions felt to be associated with treatment, and other contraindications (see Table 3) and will be excluded from taking drug if such a history is reported.

Adverse event monitoring of SAEs potentially related to AL or DP will occur passively. Subjects will be instructed to seek care at their local health facility if they experience any serious adverse reactions that may be related to AL or DP. Health facility physicians will determine if a participant should continue or stop treatment due to safety concerns. Health facility staff will be asked to notify study staff of all adverse events. For any adverse events that are reported in either arm, we will attempt to assess causality by collecting additional data on the relationship between the drug and the event. This information will be reported and reviewed by the Pharmacovigilance and Adverse Drug Reactions Committee (the Data Safety & Monitoring Board for this study).

8.2 Definitions

- Serious adverse event (SAE): An experience that results in (1) death during the study period; (2) 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, (4) specific medical or surgical intervention to prevent one of the other serious outcomes listed above.

- Suspected Unexpected Serious Adverse Reactions (SUSAR): An adverse drug reaction that is suspected of having a causal relationship to the trial medication and is unexpected

8.3 Passive identification of SAEs

Participants will be instructed to seek care at the nearest health facility if they develop a serious illness (see Appendices E & F). Also, the national emergency '977 Hotline' can be used to allow participants to receive care for urgent medical conditions. Health facility physicians, in consultation with the study physician, will decide if a participant should continue or stop treatment due to safety concerns. For less serious symptoms, participants should contact the attending study nurse to advise and quickly attend to the participant's needs. Study personnel will assist with referrals as needed. Participants will be instructed to notify their attending Study Nurse with any adverse events that may be related to either AL or DP. Health facilities will also be notified about the study and asked to call the attending Study Nurse who will be available by telephone 24 hours/day, 7 days/week.

For any potential serious adverse events that are reported in either arm, the study team will arrange follow-up visits within 24 hours at a convenient location (at home, school, or a health care facility) to complete an SAE form. This information will be reported to and reviewed by the Pharmacovigilance and Adverse Drug Reactions Committee.

8.4 SAE report forms

For each serious illness identified, an adverse event report form will be completed (Appendix S). The following information will be recorded for all experiences that are reported:

- Description of the subject (ID number, age, gender, weight)
- Name of the event
- Description of the event and management of illness
- SAE criteria met
- Date of event onset, date of resolution, and date event reported
- Maximum severity (Appendix T)
- Causality and expectedness
- Drug history (names, doses, dates administered for all drugs taken one month prior)
- Past medical history, including known allergies
- Management and outcome of the event

8.5 Expedited reporting of SAEs and SUSARs

All reports of serious adverse events that are classified as at least 'possibly' related to administration of study drugs, including those classified as possibly, probably, or definitely related, and reports of all suspected & unexpected serious adverse reactions will be entered into a database and a listing of these events will be submitted to the IRBs, the Pharmacovigilance and Adverse Drug Reactions Committee, and the drug manufacturer according to their guidelines for expedited reporting.

8.6 Management of participants with SAEs

If a study participant experiences a 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. Health facility workers may consult with the Study Nurse or the Study Physician. 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 physician colleagues to review associations and severity.

9 Follow-up surveys

9.1 Overview

Prior to implementing the intervention in each Target Area, a baseline blood survey will only be conducted in the RACD arm. Blood testing will not be performed pre-intervention in the TPE arms as the trial was designed to be operationally relevant so that feasibility (coverage, acceptability, etc.) could be assessed. In both the TPE and RACD arms, a follow-up blood survey will be conducted toward the end of the study during the end-line survey, expected to take place mid 2017. In index and secondary cases and a subset of RDT-negative control subjects from the RACD arm, a follow-up survey will also be conducted at 6-9 months for serological assessment. Finally, using routine health facility data from blood draws in symptomatic individuals, incidence data will be collected for the entire study period. Locality level incidence data will be collected over the entire study period.

9.2 Follow-up blood survey at 6-9 months

About 6-9 months after the intervention, all index cases, secondary cases, and two controls for every case will be targeted for blood collection by 250uL microtainer as well as a DBS. Samples will be labeled with a barcode and the date of sample collection. Controls must report no known history of malaria within the last year and will be matched to cases by age, gender, and geography. Study staff will return for up to 2 additional visits to ensure high capture. These samples will be used to study antibody kinetics and refine our current serologic panel of markers of recent versus past exposure in low endemic settings. This serological panel will be used in the end-line survey at the end of the study, expected mid 2017, to measure

seroprevalence. More broadly, this information will help inform future tools used in Swaziland to measure exposure and document interruption of transmission.

9.3 End-line survey (at the end of the study, expected mid 2017)

Towards the end of the study, all residents of Target Areas will be requested to participate in blood collection by DBS. Subjects who did not participate in the intervention are eligible for participation as the goal of the study is to evaluate the impact of the intervention on the community level. In addition to blood collection, we will ask a few short questions about malaria exposure since the intervention. The same barcode will be used to label the blood sample, linking the sample to the same participant. The date of collection will also be used to label the blood sample to differentiate this blood sample from previously collected blood samples (Appendices H & I). Study staff will return for up to 1 additional visit to ensure high capture.

The main purpose of the end-line survey is to perform serology. A serological assessment looking at markers of recent exposure will enable comparisons of recent transmission (and thus impact of RACD vs. TPE) between the two arms. A serological assessment looking at markers of past exposure will enable comparisons of baseline exposure between the two arms. We will also use this measure to look at antibody kinetics (in relation to the baseline and 6-9 month capture points). These samples will also be used to measure infection prevalence.

While the total sample size for the study is expected to be 6000 based on RACD data, we anticipate that 10% of these encounters will occur in individuals that will have received the intervention twice (repeat Target Area enrolled more than 5 weeks since the prior RACD intervention, or more than 8 weeks since the last TPE intervention). These individuals only need to be sampled once. Therefore, we expect to screen about 5400 individuals. While some may not be present to participate in the end-line survey, we expect to also recruit new individuals who were not previously present at the time of the intervention. This sample size will enable us to detect a difference of 3% seroprevalence in the TPE versus 0.6% in the RACD arm (Table 8).

9.4 Passive collection of incidence data

Incidence data from each locality will be collected passively for the entire study period starting from the first incident case reported in that locality. As this data will be de-identified and is part of standard surveillance, IRB approval will not be necessary for this data collection. Incidence data will be collected as: incidence of local cases (not counting the first case), proportion of imported cases (a surrogate measure of Rc [27]), and time to first end-line local incident case.

10 Acceptability Assessment

10.1 Background and Rationale

For the quantitative portion of the Acceptability Assessment, acceptability of TPE versus RACD will be evaluated by comparing refusal rates and analyzing answers from a short survey.

This qualitative portion of the Acceptability Assessment proposes to explore the acceptability of TPE from two vantage points; 1) among study participants and participants and 2) among members of the RACD and TPE surveillance teams. We will target only members of the TPE arm for acceptability assessment since RACD is the current standard in this setting and acceptability has been high. Additionally, the surveillance team will participate in qualitative exercises to enhance understanding of acceptance and refusal during the study given their constant exposure to community members offered the interventions. The results of the Acceptability Assessment will be used to refine strategies for malaria elimination in Swaziland and other malaria-eliminating settings.

We will use focus group discussions (FGDs)to understand participants situational perspective in regard to the clinical trial [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 successfully used FGDs to capture important information regarding community acceptability of new treatment modalities [30, 31]. All data will be collected by members of the field surveillance team who are native SiSwati speakers.

We will conduct the Acceptability Assessment with community participants approximately 7-10 days after an intervention (during the follow-up pill count) has occurred in a TPE community with a positive malaria case. We anticipate enrolling participants in the TPE arm for the duration of the study. We will conduct the acceptability assessment with the malaria surveillance team every 3 months for the duration of the study, beginning 3 months after the study launch.

10.2 Aims of the Acceptability Assessment

Aim 1: To compare refusal rates between the RACD and TPE arms. A short survey of those who refuse testing or treatment will be administered at the time of refusal. The short survey of refusers will ask questions about past participation in malaria screening and reasons for refusing participation in this clinical trial.

Aim 2: To understand reasons for adherence among TPE study participants receiving treatment without testing.

To appreciate the reasons for accepting TPE, we will identify study participants to explore acceptability of both practices. Methods will entail FGDs with community members who have agreed to participate in the clinical trial. The FGDs will explore past experience with malaria testing, impact of testing or treatment on daily life, and beliefs surrounding malaria transmission and possible elimination.

Aim 3: To explore the surveillance team's perception of community acceptance of RACD versus TPE.

During the clinical trial to compare RACD versus TPE around positive malaria index cases, the field surveillance team interacts with the community members to facilitate the study. Using FGDs, we will explore the acceptability of both arms of the clinical trial from the vantage point of these field surveillance team members. FGDs will be used to explore their experience consenting participants for the study and reasons community members agree or disagree to receive testing and/or treatment.

10.3 Methods for the Acceptability Assessment

Aim 1:

At the time of refusal, we will ask all community members who refuse participation in either study arm to answer a short survey. The survey will be administered by the surveillance team member on site and uploaded to an excel spreadsheet during the study. These surveys will be anonymous and take approximately 5-10 minutes. Questions include but are not limited to: "Have you ever refused to take part in a malaria screening in the past?" "If yes, why did you refuse?" "Has anything in the past with medication influenced your decision not to participate in the intervention?" (Appendix V). Participation will be completely voluntary and all refuser information will be de-identified before analysis. Information from the short survey will be evaluated during the study so that information may be used to inform the study team activities. Information from the refuser survey will be aggregated and reviewed by the study team to identify any apparent reasons for refusals.

Aim 2:

From each TPE study locality, we will ask participants if they agree to be part of a group discussion 7-10 days after the intervention (at the pill count follow up visit). From those we will choose 3-7 study participants at each site to form a focus group. As we intend to conduct a FGD in all TPE study localities beginning at the study launch, we anticipate a total of 30 FGDs during the course of the study. FGDs will be conducted 7-10 days after the TPE intervention; therefore data collection will take place on a rolling basis throughout the study. Our intent is to capture information for the duration of the study and begin analysis with the first focus group. We will evaluate changes in community uptake over time by using an iterative approach to analysis.

The goal of Aim 2 is to understand why TPE community members agree to participate in interventions around a malaria index case. FGDs will be audio-recorded and the interviewers will take notes during the sessions. Interviewers will consist of two members of the field surveillance team who are native siSwati speakers. All FGDs will take place in the village where the participants reside and be audio-recorded with written consent from the study participant. FGDs will last an estimated 1 hour and we will inquire about the participants' experience with the interventions, their personal history of malaria, their experience with testing and treatment and the impact of these interventions on daily life. Sample questions include but are not limited to: "Have you ever been part of the NMCPs screening for malaria in affected communities?" "How was your experience with the screening test done by the NMCP officers?" What do you think about getting tested for malaria before you take medication? Is it important? Why or why not?" "How did the medication make you feel after taking it?" (Appendix W). Afterwards, the audio-recordings will be translated, transcribed and a brief summary will be written for each interview. We will upload and code the FGDs transcripts using an analytical software program, ATLAS.ti5, with the assistance of the study team. Major themes will be identified by two members of the study team independently. Any discrepancies will be resolved by inviting a 3rd member of the study team to verify findings. Data will then be analyzed to provide a description of the barriers and facilitators to participation in TPE. The themes that emerge will enable us to design future interventions to improve elimination strategies.

Aim 3:

Qualitative methods described in Aim 2 will be employed in Aim 3. However, the goal of Aim 3 is to explore how members of the study surveillance team (who interact with community members enrolled in both the RACD and TPE arms) perceive community acceptance of the interventions (Appendix X). We will conduct FGDs with the entire surveillance team every 3 months, beginning 3 months after the study launch and continue for the duration of the study. FGDs will be conducted in siSwati and led by a member outside the surveillance group who is indirectly involved in the study. All participants will provide written informed consent prior to the conduct of interviews. The FGDs will be semi-structured and will focus on the observations of these surveillance team members during the study. Specifically, we will focus on their experience consenting participants for both intervention arms, reasons community members gave for accepting or refusing participation, experience with DOT and their perceptions of how to engage community members in malaria elimination strategies. The FGDs will last an estimated 1 hour. All interviews will be audio-recorded with written consent from the participants, then transcribed and uploaded to Atlas.ti for management and analysis. Participants will be assured that their responses will not impact their position on the surveillance team. Data will then be analyzed to identify major themes associated with the acceptance of malaria elimination strategies by both community members and surveillance team members. Ultimately, 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.

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
1: Refusers	All eligible residents of the TPE arm who refuse participation	• Male and female refusers at time of study intervention • Agrees to a short anonymous survey	• Resides in RACD study locality • Age <18 years • Refusal to participate in the refuser survey
2: FGDs with TPE study participants	Non-index cases residing within TPE study localities, 3-7 participants per FGD, anticipate 30 TPE study localities over duration of study.	• Male and female participants • Residents of index household • Residents of neighboring households • Provide informed consent (participants)	• Resides in RACD study locality • Refusal to participate in the Acceptability Assessment • Speaks language not understood or able to be translated to interviewer. • Age < 18 years
3: FGDs with TPE & RACD surveillance team members	All members of the surveillance team in both TPE & RACD study arms	• Provide informed consent	• Refusal to participate

11 Cost-effectiveness assessment

The goal of the cost effectiveness assessment will be compare TPE versus RACD in terms of costs per response or incident case of as well as cost per population and case averted as measured through the difference in asymptomatic and symptomatic infections identified at the end of the intervention. Our hypothesis is that the costs of TPE versus RACD will be lower due to the cost savings from not performing a diagnostic test as well as the cases averted due to higher effectiveness to prevent future infections.

We will collect detailed expenditure data on costs of delivery of TPE and RACD interventions. Calculations will include costs for all consumables as well as staff time, which will be prospectively collected every 10th TPE or RACD event.

12 Laboratory procedures

12.1 Rapid diagnostic tests

Pf-specific RDTs (First Response) will be performed on participants every time a blood sample is collected. RDTs will be performed according to the directions provided, using the blood transfer device and reagents provided by the manufacturer. Tests will be performed by study personnel, and results will be available within 15 minutes. The results of the RDT 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 brought to their local health care facility for appropriate work-up and treatment with AL.

12.2 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 25µl aliquots per blood spot (4 blood spots per sample). Filter paper samples will be labelled with the individual's bar code 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 zip lock bag and will be placed into a stock card filter paper box for final storage at -20°C.

12.3 Microtainer blood collection

Microtainers with dry EDTA anticoagulant will be used to collect 250µl of blood for research purposes only. This blood will be collected from secondary cases identified at the RACD intervention visit during case investigation. Microtainer blood samples will also be collected from index cases, secondary cases, and a sample of RDT-negative controls at the 6-9 month follow-up survey. Whole blood samples may be stored at 4°C for up to 24 hours before centrifugation to separate plasma from blood cells.

12.4 Antibody and DNA extraction

Antibodies and DNA will be extracted from dried blood spots using the Chelex method with saponin.

Whole blood samples (collected at the 6-9 month Follow-up visit and at the end-line survey visit near the end of the study, expected mid 2017) should be centrifuged within 24 hours to separate out the plasma. Pelleted blood cells will be resuspended with PBS buffer, and can be stored at 4°C for up to one week before DNA is extracted using a Qiagen blood extraction kit at the National Reference lab for the appropriate molecular tests.

Plasma and DBS antibodies will be stored in cryovials ideally at -20°C or lower. DNA will be stored in cryovials at -20°C.

12.5 LAMP

DNA samples will first undergo LAMP testing using the Pan-LAMP detection kit (which detects DNA sequences common to all *Plasmodium* species), followed by testing with the *Pf*-LAMP detection kit if Pan-LAMP positive. These studies will be performed only for research purposes and will have no impact on the clinical management of study participants.

12.6 PCR

All RDT or LAMP positive samples as well as 10% of negative samples will undergo nested cytochrome B PCR testing with species specific identification using a restrict digest,.[8–10][32] Other molecular studies may include analyses of polymorphisms in parasite and/or human genes for mutations that may impact on clinical malaria, and genotyping of malaria parasites. These studies will be performed only for research purposes and will have no impact on the clinical management of study participants.

12.7 Genotyping

Genotyping of *Pf* will consist of a panel of microsatellites and/or 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 tagged primers, and sized using denaturing capillary electrophoresis. Multi-locus genotypes from mixed infections will be reconstructed, where possible, by quantifying alleles at each locus. Genotyping of additional loci will be performed as needed. These studies will be performed only for research purposes and will have no impact on the clinical management of study participants.

12.8 QT-NASBA for gametocytes

RNA will be extracted from DBS using the Boom extraction method.[33]Sub-microscopic gametocyte density will be measured using the *Pf* 25S mRNA real time QT-NASBA.[34] These studies will be performed only for research purposes and will have no impact on the clinical management of study participants.

12.9 ELISA

Serology, a test of past infection as assessed by the presence of antimalarial antibodies, may improve the identification of hot spots. ELISA assays will be performed using previously described methods[6]. Briefly, plasma or DBS antibodies will be assayed to detect antibodies against the *Pf* blood stage antigens merozoite surface protein-1 ($MSP\text{-}1_{42}$) and apical membrane antigen-1 (AMA-1), both biomarkers of *P. falciparum* exposure.[35] Other antigens that are sensitive and specific for recent exposure (currently undergoing evaluation) may also be used. ELISA assays will be performed in duplicate and optical densities recorded with an ELISA reader. Other serologic platforms (bead array, protein microarray) may also be used

analyze responses to multiple antigens if available. These studies will be performed only for research purposes and will have no impact on the clinical management of study participants.

12.10 Sample storage for future studies (for research purposes only)

After the study period, samples will be stored for future research. The consent forms for this study include a statement about future testing for research purposes only. Samples will be stored for 25 years, reason being that if there are new malaria cases after elimination, it will be helpful to have past samples for molecular testing. The WHO recommends an isolate bank because comparing new strains to past strains will help distinguish between imported and local infection[36]. Re-emergence of new cases could occur more than 20 years after elimination. For example, North and South Korea eliminated malaria in the 1970s, but then experienced a re-emergence of the disease in the 1990s.

13 Data management

13.1 Quality assurance & quality control

All members of the 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 members 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. Study group meetings will be conducted by the principal investigator 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.[37] The correction will be initialed and dated by the investigator.

13.2 Records & storage

The principal investigator 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, when not in use, and the key kept by the local investigators. Participants will be identified by their study ID number, and participant names will not be entered into the computerized database. Data will be stored for at least 5 years. Authorized representatives of the sponsor, the ethics committee(s) or regulatory bodies may inspect all documents and records required to be maintained by the investigator. The investigators will allow all requested monitoring visits, audits or reviews.

14 Statistical issues

14.1 Study population

Overall:

Based on the most recent census data, the overall population in the 77 study localities is estimated at 211,189 individuals. However we expect that some localities will have no incident cases and therefore not receive any intervention. In the previous two transmission seasons, only 63 of the 77 localities had at least one case. Our sample size calculations are further based on the expected at-risk population within the 63 localities, or EA that had at least one case in the previous three seasons, a total of 55,928 individuals. The size of the expected at-risk within localities varies greatly, therefore we used the harmonic mean of

population size in localities with at least one case (656 per locality) to represent the effective sample size of the study in calculations of the design effect.

Target Area:
As defined above in section 4.4, the Target Area for TPE localities is defined as all individuals residing within 200m of an index case that is detected in passive surveillance and resides in a TPE study locality, with individuals residing immediately beyond 200m included if a minimum of 30 enrolled individuals is not reached within 200m. The Target Area for RACD localities is defined as all individuals residing within 500m of an index case that is detected in passive surveillance and resides in a RACD study locality. Sample size calculations for the secondary outcome measures of seroprevalence and infection prevalence are based on the population of the Target Areas.

The sample size for the Target Area assessments is estimated from incidence in the previous transmission season, and the expected drop in incidence among those in the TPE arm; resulting in an estimated 200 index cases total with 30 individuals screened or treated in the Target Areas around each case. With 200 index cases, we expect about 6000 encounters where individuals will receive a study intervention (either TPE or RACD). Based on preliminary RACD data, we anticipate 10% of these encounters will occur in individuals who previously received an intervention during the study period (repeated or overlapping Target Areas). For the follow-up end-line seroprevalence survey, these individuals will only be sampled once. Thus the effective sample size for the seroprevalence outcome measured in the Target Area population is expected to be 5400. Of note, the first index case for each Target Area will not be included since this person's malaria exposure occurred pre-intervention.

For the follow-up end-line infection prevalence survey, index cases will also be included as they will also be at risk for subsequent infection. Thus the effective sample size for the infection prevalence outcome measured in the Target Area population will be 5400 individuals screened plus 200 index cases, or 5600 individuals.

Adherence evaluation:
Adherence will be measured on a subsample that includes only the individuals in the Target Areas surrounding the first index case in each locality. We expect that 22 localities in the TPE arm will have at least one index case, and at least 30 individuals will be assessed for DP treatment per Target Area, for a total sample of 660 individuals.

14.2 Outcome measures

Table 6. Outcome measures

Outcome	Indicator
Primary Aim	
Incidence	Cumulative incidence of all cases (*Pf* infection) identified by passive surveillance in the locality subsequent to the first reported case during the study period (not including additional cases found through RACD). Cases include both locally acquired and imported infections.
Secondary aims (effectiveness)	
Exposure (seroprevalence)	Seroprevalence to markers of recent exposure using ELISA in end-line survey samples taken from residents in Target Areas near the end of the study (expected mid 2017), excluding index cases detected through passive surveillance.
Infection prevalence	Prevalence of infection by LAMP and QTNASBA testing for gametocytes in LAMP positives in end-line survey samples taken from residents in Target Areas near the end of the study (expected mid 2017), including index cases detected through passive surveillance.
Time to first local post-intervention incident case	Time to first incident local case in the Target Area subsequent to the intervention. Target Areas that receive a repeat intervention will qualify to be included again at subsequent interventions.
Proportion of imported incident cases	Proportion of imported incident cases in the locality subsequent to the first reported case will be measured through passive surveillance. Additional cases found through RACD will not be included.
Transmission potential (by genotyping)	Microsatellite genotyping will be performed on samples collected from index cases as well as secondary cases.
Secondary aims (feasibility)	
Coverage	Proportion of persons residing within approximately 200m (TPE localities) or 500m (RACD localities) of the index case who consented to participate in the study and who completed the initial procedures for their study arm (finger prick for RDT in the RACD arm, initial dose of DP in the TPE arm)
Adherence	Proportion of persons who completed 3 days of therapy among all individuals initiated on DP in the TPE arm, as assessed by pill count
Prevalence of SAEs related to treatment	Proportion of subjects experiencing SAEs deemed possibly, probably, or definitely related to DP or AL, out of the total number of subjects enrolled
Acceptability	Qualitative assessment (See Section 10)
Cost	Cost per index case-level intervention, cost per case averted.

14.3 Estimates of study power

Sample sizes and design effect estimates:

Sample size was driven by the number of localities within the area in the country considered to be at-risk for malaria transmission and the number of index cases we expect will be identified within those localities during the study period. The overall, Target Area, and adherence evaluation samples are described above in section 14.1. To estimate power to detect differences in cumulative incidence we used sample size of 55,928 for the overall sample. To estimate power to detect differences in seroprevalence, we used sample size of 5400 for the Target Area sample based on the assumptions as described above. As noted we used harmonic means for locality size (cluster size) in our estimates of power and design effect rather than arithmetic means to estimate more conservatively and to reduce the impact of the few localities with large population sizes.

We conducted sample size calculations to determine our ability to detect a difference in the effectiveness of TPE compared to RACD on incidence. We used the equations suggested by Hayes and Moulton (Cluster Randomized Trials, CRC Press, 2009) to calculate sample size required to detect a difference between arms.

Calculations are made for differences in proportion and assuming a coefficient of variation of 0.9 based on census and surveillance data from September 2012 to March 2015 to estimate the number of localities with cases, index cases and cluster size as described above. The power calculations are sensitive to sample size, but—in our study—the cluster population size is fixed. Sample sizes for primary and secondary outcomes can be found in Table 9.

Primary outcome – Cumulative Incidence:

Our primary study outcome is cumulative incidence of passively detected malaria infections in the overall population of the randomized study area localities. If incidence in the RACD arm remains as it was during the 2012-2015 transmission seasons (during which RACD was the standard of care) then given the above assumptions, we would expect cumulative incidence in the RACD arm to be 0.4% or approximately 4 per 1000 persons. If this is the case, our study would have 80% power to detect a reduction in cumulative incidence to 0.2% or 2 per 1000 persons if at least 51 of the 77 study localities had at least one index case (Table 7). Should cumulative incidence in the RACD arm rise to 0.5%, the reduction to 0.25 or 2.5 per 1000 persons in the TPE arm would be detectable with at least 47 localities with at least one case. Should cumulative incidence in the RACD arm fall to 0.3%, reduction to 0.15% or 1.5 per 1000 persons in the TPE arm would be detectable with 57 localities with at least one case. Because of the clustered nature of the data and the variability in cluster size, we used the harmonic mean of the population size (656 per locality, or 41328 total population using the harmonic mean of locality population).

Secondary outcome of effectiveness – Seroprevalence:

In the end-line survey near the end of the study (expected mid 2017), non-index cases residing in Target Areas will undergo blood testing to measure seroprevalence. Index cases will also be included as long as they were not the first index case for a Target Area. The first index case will not be included as this person's malaria exposure was known to occur pre-intervention. The sample size for the seroprevalence measure is expected to be 5400. Based on preliminary data, we expect seroprevalence to be approximately 3% prior to any intervention.[6]

End-line seroprevalence for RACD was calculated based on an estimate that only 20% of individuals with infection will be detected by RACD and treated, leading to a 20% effectiveness of RACD, or a drop from 3.0% pre-intervention to 2.4% end-line seroprevalence. We believe that TPE will be more effective than RACD in reducing seroprevalence near the end of the study (expected mid 2017). Because of the clustered nature of the data and the variability in cluster size, we used the harmonic mean number of observations expected per locality (60) to generate the effective sample size for analytic power (3780). Using these assumptions, our study would have 80% power to detect a decrease in seroprevalence to 1.18% in the TPE arm if 63 of the 77 localities had at least one case (Table 8).

Secondary outcome on feasibility – Coverage:

For the feasibility outcome measure on coverage, estimates were based on the goal TPE coverage of 80%. This goal is based on modeling data which suggests at least 80% coverage is needed for MDA to be successful, as well as experience from some settings that have successfully interrupted transmission in the setting of MDA [8, 18]. If estimates of incidence in the TPE arm are accurate, approximately 66 index cases will be identified and 1782 individuals will be treated in the TPE-assigned Target Areas. If the true coverage is 80% coverage, we would have a 95% confidence interval between 77% and 83% with this sample size [38].

Secondary outcome on feasibility – Adherence:

To measure adherence to DP, we will perform a pill count in individuals residing in the first Target Area for each TPE locality each transmission season. We will have 5% absolute precision to detect 80% adherence when the sample size reaches 532. If adherence is lower than expected, we will still have 10% absolute precision to detect 50% adherence when the sample size 208.

Table 7. Detectable Reductions in cumulative incidence given different assumptions about Incidence in the RACD

# Total localities with at least one index case	# localities per arm	Number assessed per locality (n)		Cumulative Incidence		Km (coeff of variation)	Z beta	Power
		RACD	TPE	RACD (π_{0})	TPE(π_1)			
47.0	23.5	656	656	0.500%	0.250%	0.9	0.84	80%
50.6	**25.3**	**656**	**656**	**0.400%**	**0.200%**	**0.9**	**0.84**	**80%**
56.6	28.3	**656**	**656**	0.300%	0.150%	**0.9**	0.84	80%
61.4	30.7	**656**	**656**	0.250%	0.125%	**0.9**	0.84	80%
68.5	34.3	**656**	**656**	0.200%	0.100%	**0.9**	0.84	80%
80.5	40.2	**656**	**656**	0.150%	0.075%	**0.9**	0.84	80%

Based on equation 4 from Hayes and Bennett International Journal of Epidemiology 1999;28:319-32

Assumes that population is only those in the EAs that have at least one case.

Sample size calculation based on harmonic mean of population size.

Table 8. Detectable reductions in seroprevalence given varying assumptions about prevalence in the RACD arm

# Total localities with at least one index case	# localities per arm	Number assessed per locality (n)		Outcome proportion		Km (coeff of variation)	Z beta	Power
		RACD	TPE	RACD (π_{0})	TPE (π_1)			
46.6	23.3	60	60	3.00%	1.35%	0.9	0.84	80%
62.3	**31.2**	**60**	**60**	**2.40%**	**1.18%**	0.9	**0.84**	**80%**
49.3	24.7	60	60	2.00%	0.83%	0.9	0.84	80%
50.8	25.4	60	60	1.50%	0.57%	0.9	0.84	80%

Based on equation 4 from Hayes and Bennett International Journal of Epidemiology 1999; 28:319-326

Assumes we are including only persons in the target areas in the denominator but evaluating at locality level

Assumes 3 per 100 is the background seroprevalence

Table 9. Sample sizes for primary and secondary aims.

Outcome	**Result***	**Actual sample size (Effective sample size, based on harmonic mean in clusters)**
Primary aim		
Incidence	0.4% (RACD) vs. 0.2% (TPE)	55,928 (41,328)
Secondary aims (effectiveness)		
Exposure (seroprevalence)	2.4% (RACD) vs. 1.18% (TPE)	5400 not including index cases (3720)
Infection prevalence	n/a	5600 includes index cases
Time to first post-intervention incident case	n/a	55,928 (41,328)

Outcome	Result*	Actual sample size (Effective sample size, based on harmonic mean in clusters)
Proportion of imported incident cases	n/a	55,928 (41,328)
Transmission potential	n/a	Genotyping estimated to be performed in 800 index cases** and 35 infections from follow-up cross sectional survey
Secondary aims (feasibility)		
Coverage in TPE Arm	80% (95% CI: 77%-83%)	1782
Adherence in TPE Arm	80%	532
Prevalence of SAEs related to treatment	n/a	5400 not including index cases (3720)
Acceptability	n/a	5400 not including index cases (3720)
Cost	n/a	10 Target Areas/arm

*for some secondary outcomes, power calculations were not performed however effective sample size is shown.
** 200 index cases will be from the study area but an estimated 600 DBS that are already collected as standard surveillance from other parts of the country will also be used to characterize the background genotypes/transmission potential in Swaziland, as it relates to the transmission potential in the study areas.

14.4 Analytical plan

Preliminary Analyses 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 yield valuable descriptive findings that will characterize coverage and cluster and Target Area characteristics in the study population. These analyses will also be stratified by randomization group (i.e., TPE vs RACD) using cluster-based two-group comparison methods (e.g., Rao-Scott chi-square) to check the equality of group covariates at baseline. Although we expect the randomization to produce balanced covariate structures, we will consider methods of adjustment to balance baseline covariates should there be significant differences between the TPE and RACD groups. To look for areas where there is a possibility of contamination by proximity of index cases assigned to different arms, we will describe the distances between TPE and RACD assigned index cases as well as the number of RACD assigned index cases who were within 2km of an index case assigned to TPE.

Primary Analysis:
For the primary analysis comparing incidence between the TPE and RACD arms, we will follow an intention-to-treat (ITT) approach. We hypothesize that cumulative incidence in the TPE localities will be lower than in the RACD assigned localities. For the initial ITT analyses, estimates of effect will be unadjusted for any variables other than intervention group. To check for possible contamination of effects by proximity to an index case treated with TPE, a second set of ITT analyses will be conducted adjusting for intervention group and distance of index case from an index case assigned to TPE. Outcomes are assessed at the individual level. Because of the clustered nature of the data, our modeling approach will also adjust for correlation of observations by locality for analyses using the overall sample and by locality and index case 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 localities. GEE estimates are consistent even if the correlation structure is miss-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 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 miss-specified. Alpha will be set at 0.05 for all planned comparisons.

Should the preliminary analyses reveal an imbalance in the baseline covariates between the TPE and RACD 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.

Subgroup analyses: Although there is limited power with our constrained sample size, we will describe summary measures of incidence and intervention effects for some specific subgroups of interest within our study area population. Of particular interest are those who did or did not have insecticide spraying of their household areas, strata of risk as determined by the National Malaria Control Program, and season of index case presentation.

Secondary analyses:
Assessments of secondary outcomes will also 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 individuals in the Target Areas who will be participating in blood testing surveys conducted towards the end of the study (expected mid 2017). As noted, for analyses of outcomes in the Target Area sample, clustering by both locality and index case area will be accounted for in the modeling approach. To account for possible contamination by proximity to another index assigned to the TPE arm, models will also include adjustment for distance to the nearest index case treated with TPE. Planned secondary analyses and hypotheses are as follows:

Hypotheses regarding the effectiveness of TPE compared to RACD:

1. Comparison of seroprevalence using antibodies to markers of recent exposure. Using the samples collected in the end-line survey near the end of the study (expected mid 2017), we expect that seroprevalence will be lower in the Target Areas receiving TPE than in those receiving RACD.
2. Comparison of prevalence of malaria infection. Using the samples collected in the end-line survey near the end of the study (expected mid 2017), we expect prevalence to be lower in the Target Areas receiving TPE than in those receiving RACD.
3. Comparison of proportion of incident cases that are imported. We expect that local transmission will be reduced by TPE and thus the proportion of subsequent cases imported will be higher in the TPE arm than in the RACD arm. This outcome will be summarized at the locality level and analyzed with locality as the unit of analysis.
4. Comparison of time to first post-intervention incident infection. We hypothesize that time to the first post-intervention index case within the Target Area will be longer for Target Areas receiving TPE compared to those receiving RACD. Analysis for this outcome will use a standard cox proportional hazards model to estimate the time to a subsequent incident infection among individuals in the Target Area.
5. Comparison of transmission potential using genotyping. Microsatellite genotyping will be used to measure transmission potential. DNA samples for genotyping will be collected from index cases and secondary cases. Based on malaria rates in Swaziland over the past three years, we expect approximately 200 index cases over the study period and 35 infections from the follow-up cross sectional survey (1.6% prevalence in the TPE arm and 0.4% in the RACD arm). We expect transmission potential to be lower in the TPE versus RACD arm. Relatedness of infections within Target Areas and within localities will be used as a surrogate for transmission potential.

Planned Analyses of Operational Feasibility and expected findings:

1. Coverage of the intervention. The numbers and proportion of the population completing finger prick testing (if RACD arm) or receiving at least the first dose of medication (if TPE) will be calculated by arm. The proportion of the individuals living in Target Areas around an index case that receive the TPE intervention is expected to be 80% with a 95% confidence interval from 76% to 84%.
2. Adherence to TPE. In the subsample of Target Areas surrounding the first index case in each locality assigned to TPE, we will assess adherence to the 3 day regimen of DP in TPE using pill count. We expect adherence to be 80%.
3. Safety of the TPE treatment. The number and percent of individuals experiencing an adverse event will be recorded by study arm. We expect that compared to RACD, TPE will be safely administered with few or no serious adverse events related to treatment, and no difference in SAEs compared to AL based on analysis of the adverse events report forms.
4. Acceptability of the intervention. See Section 10.
5. Costs per incident infection and per population. Detailed costing will be performed in 10 Target Areas per arm. We expect that costs per incident infection and per population for implementing the TPE intervention will be no higher than for RACD, the current standard of care.

15 Advisory Committee

15.1 Role of the Advisory Committee

The role of Advisory 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 Advisory Committee will provide oversight to ensure that the research is well coordinated, scientifically and ethically sound, and in line with the Ministry of Health's goals for elimination in Swaziland. Not all committee members are expected to be directly involved in the project.

15.2 Membership of Advisory Committee

The General Committee of the Swaziland Malaria Elimination Advisory Group (SMEAG) will serve as the Advisory Committee for this study. The SMEAG was established in 2010 to establish policy, to provide technical guidance on implementation of policies, and to monitor policy implementation and progress toward elimination. The SMEAG includes senior representatives from major partners to the NMCP including the World Health Organization (WHO), United Nations Children's Fund (UNICEF), CHAI, UCSF, the Swaziland National Association, the Swaziland Medical and Dental Association, Swaziland Nurses Association, Red Cross, and University of Swaziland (UNISWA) (Appendix Y). To provide additional technical expertise as well as a global perspective, senior representatives from UCSF Department of Medicine and the Bill and Melinda Gates Foundation will also be invited to join in meetings about this study.

15.3 Activities of the Advisory Committee

The Advisory Committee will meet once yearly in Swaziland to review and provide recommendations this project. The first meeting will serve to review and approve the protocol. Subsequent meetings will be to report on progress and review data. International members of the Advisory Committee will be encouraged to join meeting in person, however may join by teleconference if schedules limit travel to Swaziland. Advisory Committee members will also have ongoing interactions with study team members on an as needed basis.

16 Data and Safety Monitoring Committee

16.1 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee (the Pharmacovigilance and Adverse Drug Reactions Committee) will be assembled in conjunction, consisting of a minimum of four members who are independent of the project and who have made no significant input into the project's design. Members will include experts in statistics, epidemiology, clinical trial design, and include at least one local clinician. One member will serve as the Chair of the Committee and one will serve as the Secretary. Depending on the agenda, independent advisors or experts can be invited to the meeting, upon approval by the chair and secretary. The Committee, investigators, and the sponsor 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. The Committee will review the study protocol and analytical plan prior to the onset of the study, and will review SAE and SUSAR reports during the course of the trial. The Committee will also assess cumulative SAE throughout the course of the study to assess study safety and make decisions on necessary protocol changes. Full details in the Terms of Reference (Appendix Z).

16.2 Meetings

An initial meeting will be held to introduce the project to committee members. Following this introductory meeting, the committee will meet at regular agreed upon intervals. These meetings will be planned around observed and regular reports of suspected adverse drug reactions. Committee members are expected to attend meetings 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. However, the busy schedules of members will be respected and meetings convened their availability.

16.3 Stopping guidelines

Decisions about discontinuation of the study will be made by the members of the Committee. Stopping guidelines will be based on the prevalence of serious adverse events (for the TPE vs. RACD groups) deemed to have a causal association with study drugs.

17 Ethical considerations

17.1 Institutional review boards

This protocol and the informed consent documents and any subsequent amendments or modifications will be reviewed and approved by all institutional review boards (IRBs) before the study begins, including the Swaziland Ministry of Health Ethics Committee and the UCSF Committee for Human Research. A Data and Safety Monitoring Committee (the Pharmacovigilance and Adverse Drug Reactions Committee) will be established to oversee the trial.

17.2 Informed consent process

Approval from local leaders will be sought before beginning activities in the project area. All informed consent discussion will be conducted in SiSwati or English and a translator will be used if necessary. All information sheets and consent forms will be available in SiSwati and English, describing the purpose of the project and the procedures to be followed, and the risks and benefits of participation. During the consent discussions, each section of the consent form will be read exactly as it is written either by study personnel or by the translator, and then further explained as necessary. Consent for future use of biological specimens for research purposes only will be obtained. All participants, parents/guardians will be informed that participation in the study is completely voluntary and that they may withdraw from the study at any time.

Written consent to participate in the research study will be documented for the relevant study procedures (Table 4). For children <18 years of age, consent will be obtained from one parent or guardian, as is customary in Swaziland. For participants between 12-17 years of age, we will also obtain minor assent as is customary in Swaziland. If the person asked to provide consent is unable to read or write, their fingerprint will substitute for a signature.

17.3 Risks and discomforts

Randomization:
In this cluster-randomized trial, half of participating communities will be randomly assigned to TPE, while half will be randomly assigned to standard of care RACD. The TPE intervention may prove to be more or less efficacious, more or less well-tolerated, and/or more or less safe than standard care. Thus, there is the risk that localities will be randomized to a less efficacious, less well-tolerated, and/or less safe study arm. However, the risks associated with randomization in this study are likely to be low.

Dihydroartemisinin-piperaquine:
DP has an excellent efficacy and safety profile, including in asymptomatics. However some adverse events that have been reported in association with DP including nausea, diarrhea, vomiting, abdominal pain, anorexia, pruritus, rash, and dizziness. An increased risk of early vomiting has been reported in children with uncomplicated malaria treated with DP, as compared to those receiving artemether-lumefantrine, however, this was reported in young children (aged 6-24 months) and was higher in those that were breast-fed.[39] In a large multicenter trial of 4116 African children under five with uncomplicated malaria, in which 1,468 children were treated with DP, the most commonly reported adverse events related to DP were anemia (6.5%) and vomiting (3.3%). Serious adverse events occurred in 10 children, but only 4 (0.3%) were felt to be related to DP. Five deaths occurred in the study; the one death in the DP arm was due to diarrheal disease.[40] A prospectively pooled analysis of six trials conducted in Asia and Africa, indicated that the risk of adverse events associated with DP was lower than with comparator ACTs, and that most adverse events were commonly reported in relation to clinical malaria.[25]

DP was evaluated for use as IPT in schoolchildren in Uganda in a trial comparing DP, sulfadoxine-pyrimethamine (SP), and amodiaquine + sulfadoxine-pyrimethamine (AQ+SP), to placebo.[11] In this study of 780 children, those receiving DP were at no higher risk of adverse events than those receiving placebo. In another recent study of IPT in schoolchildren using DP in Uganda, no safety concerns were identified. The most commonly reported adverse events in this study were cough, headache, and abdominal pain, but children receiving DP monthly or once a term were at no higher risk for these events than those receiving placebo. There was also no difference in the risk of anorexia, nausea, vomiting, diarrhea, or pruritus between the groups[21].

In general, ACTs are not recommended for use in the first-trimester of pregnancy due to insufficient safety data.[41]In second and third trimester, ACTs may be used with the exception of DP, for which safety data in late pregnancy are lacking. A recent review of published data on 945 women exposed to an artemisinin during pregnancy, including 123 during first trimester, and 822 during the second or third trimester, did not identify an association between use of artemisinins and adverse pregnancy outcomes.[41] However, these studies were limited by small sample sizes and lacked power to detect rare serious adverse events and heterogeneity between studies precluded pooled analysis.

To minimize any safety risks associated with DP treatment, we plan to exclude all pregnant or breastfeeding women as well women who have experienced menarche, but no menses in the past 4 weeks from DP treatment. Due to limited data in infants <9 months of age or <7kg, these subjects will also be excluded from DP treatment. Individuals excluded from DP treatment will be given an RDT to determine if they have a malaria infection, and will be advised to seek treatment at their health facility if they test positive for malaria. In addition, we will monitor for SAEs.

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 effects from the blood drawing, and overall the risks associated with blood draws are likely to be low. To reduce the potential risks, 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, RDT results will be provided to participants and treatment will be offered if RDT results are positive. Participants with positive tests will be referred to the local health facility and escorted by study staff when feasible. It is possible that for some cases in the community, the RDT will be negative, but the molecular test will be positive. This most commonly occurs when parasitemia is very low, below the level of detection for RDTs, but not below the level for LAMP or PCR. These subjects will not treated as the performance of LAMP or PCR is for research purposes. The risk of developing symptomatic or severe illness is very low from a presumably low parasitemia 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, without confirming the RDT result by a molecular test.

Confidentiality:

Participation in a research study may involve a loss of privacy, but successful implementation of the study will require that the confidentiality of all study participants be strictly maintained. The risks associated with loss of privacy in this study are likely to be low. To ensure confidentiality is maintained, all information gathered will be treated as private by the study personnel, and records will be kept securely in locked filing cabinets and offices. 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.

17.4 Compensation

Participants will not be paid for taking part in this study. Most assessments will be conducted at households, which will eliminate the need for travel and minimize opportunity costs for the participants. If study participants are referred by study personnel to a health facility for further assessment, transportation may be facilitated by the project on a case to case basis. Any diagnosis and treatment associated with the study will be provided free of charge.

18 Timeline

Expected outcomes and related activities	Year or Quarter Year 1 1/14-12/14	Year 2 1/15-12/15	Year 3 1/16-12/16	Year 4 1/17-12/17	Milestones
Study preparation					• Develop, review, and finalize work plan & protocol. In-country review of work plan & protocol; incorporate feedback into protocol. Finalize protocol. • Randomize ½ of localities in the receptive area to the intervention, ½ to control. Sensitization of participating localities. • Complete & submit applications to UCSF and local 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 (DP, field supplies)
					• Field team conducts case investigations & deploys RACD or TPE.
					  • RACD arm - perform RDT and refer secondary cases to health facilities.
					  • TPE arm - Administration of DP

Adverse event monitoring					• When adverse events occur, collecting 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 in RACD arm, 6-9 month blood collection for serology validation
Data collection: outcome measures					• Perform routine surveillance for incidence data, time to subsequent cases, imported/local ratio. • Collect & coordinate the end-line survey near the end of the study, expected mid 2017 (blood samples for infection prevalence and serology) • Collection operational feasibility outcome measures – coverage, safety (adverse event monitoring above), costs, adherence through pill count
Data collection: Qualitative assessment					• Finalize SOPs for qualitative assessment of acceptability. • Field team performs in-depth interviews with study participants and key informants.
Project Monitoring					• Develop and finalize SOP for monitoring project data. • Database check-ins. • Coordinate and hold annual and ad-hoc meetings of the Pharmacovigilance and Adverse Drug Reactions Committee and the Advisory Committee
Preliminary data analysis					• Develop and finalize SOP 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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Appendix A. Study information for stakeholders

An Evaluation of TPE (targeted parasite elimination) for Malaria Elimination in Swaziland - Study Information for Stakeholders

In 2007, the Swaziland Ministry of Health (MoH) established a goal to eliminate malaria. In order to interrupt malaria transmission, it is necessary to implement preventative measures (such as vector control, health education) as well as find and treat all infections, whether symptomatic or asymptomatic. Swaziland's transition from a malaria control to elimination program required the scaling up of community-based interventions including:

- Reactive Case Detection (RACD): household members and neighbors of index cases residing in malaria receptive are screened for malaria using rapid diagnostic tests (RDTS) to identify secondary infections
- Universal coverage of Long Lasting Insecticide Net (LLIN) in receptive areas: community members are provided with free LLINs and are encouraged to sleep under a net
- Indoor Residual Spraying (IRS): community members are encouraged to allow their houses to be sprayed with insecticide before and during malaria seasons.
- Promoting appropriate health seeking behavior.

Targeted Parasite Elimination (TPE), which involves the treatment of all high-risk individuals with an effective drug irrespective of and without knowledge of that individuals' infection status, has been proposed as a strategy to complement the above mentioned community strategies. The goal of TPE is to treat existing reservoirs of infection and prevent future infection through the drug's prophylactic effect. An advantage of TPE, over RACD, is that it does not depend on RDTs which often miss low density infections among asymptomatics. In collaboration the University of California, San Francisco Global Health Group (UCSF GHG), Clinton Health Access Initiative (CHAI) and other partners, MoH will pilot TPE in selected high-risk localities while studying the feasibility and effectiveness of this approach compared to RACD.

Study stakeholders in Swaziland include, but are not limited to:

- Members of the MoH
    - Swaziland Laboratory Health Services (SLHS)
    - Regional Health Management Teams
    - Rural Health Motivators (RHMs)
- Swaziland Malaria Elimination Advisory Group (SMEAG) Members
- Chiefdoms (Regional Administrators office)

Informational Sessions for National and Regional level stakeholders:
The Ministry of Health (MoH) and its national level partners are invited to attend a briefing of the proposed TPE study before its commencement on the 01st of November 2014.
Regional health management teams will be briefed during their monthly meetings before study commencement and regularly updated during study progression. As a key facet of the study includes the administration of a drug to asymptomatic community members, one goal of these meetings will be to utilize regional networks to ensure that clinical and public health workers within targeted localities are made aware of the study goals and activities.

Informational Sessions for Community level stakeholders:
Study staff will work with Regional Administrators to identify chiefdoms in study areas and their relevant leaders, including Bandlancane (community leaders committee) and clinic committees. These community level leaders will be invited to attend informational sessions about the TPE study.
Stakeholder engagement is critical to ensure successful implementation of novel community interventions such as TPE. Making all levels of the health delivery process aware of the study will provide the NMCP with the needed support to effectively deliver and engage the community in proposed interventions. Knowledge of TPE by health care workers in targeted localities will also assist with management of potential but rare adverse reactions to the study drug.

Appendix B. Index case immediate notification form

Ministry of Health

HISCC approved xx/xx/xxxx

Notifiable Conditions - Immediate Notification Form

Use the following process to IMMEDIATELY report Notifiable Conditions to the EPR Emergency line:

1) If a case is suspected, check the case definitions on the other side of this form to see if it must be notified.
2) If it is notifiable, collect the information on this form from the patient or accompanying relatives/friends.
   If there are two or more cases, fill in a separate form for each case (ie one for each patient).
3) Once the form is completed, immediately telephone the EPR toll-free line on 977 to report this case.
   Treat this as very urgent - telephone immediately. ***A call to 977 is free-of-charge from any cellphone.***
4) Follow the Additional Instructions for each specific condition that are written on the other side of this form.

PART A - FACILITY/PERSON REPORTING

Facility Name:		Report Date:	/ /
Facility Code:		Person preparing report:	
If the case is discovered in the community, please report via the nearest facility.		Cellphone contact number:	

PART B - PATIENT DETAILS

Surname:		First names:	
Sex: ☐M ☐F	Pregnant: ☐Yes ☐No	Date of birth:	/ /
Telephone contact for patient:		Chief:	
Location of patient's home: (give nearest landmark and head of household)			

PART C - DETAILS OF THE CONDITION

Please tick ALL boxes that apply to this single case/patient:

- ☐ Confirmed Malaria (RDT or microscopy)
- ☐ Maternal Death
- ☐ Perinatal Death
- ☐ Neonatal Tetanus
- ☐ Suspected Measles
- ☐ Suspected Human Rabies
- ☐ Suspected Meningococcal Meningitis
- ☐ Suspected H1N1
- ☐ Acute Flaccid Paralysis
- ☐ Viral Haemorrhagic Fever
- ☐ Suspected Rift Valley Fever
- ☐ Suspected Yellow Fever
- ☐ Suspected Typhoid Fever
- ☐ Suspected Cholera
- ☐ Suspected Severe Food Poisoning

Date of onset:	/ /	Date of admission: *(if applicable)*	/ /	Date of death: *(if applicable)*	/ /
Case comments:					

Once you have completed this form, immediately ring the EPR toll-free line on 977 to report this case.

Date/time of call:	/ / at am/pm	Your signature:	
EPR officer receiving call:			

Appendix C. Index Case, Case Investigation Form

Greetings! My name is _____. I am conducting surveillance with the National Malaria Control Program within the Ministry of Health. You or your child recently had malaria and we would like to better understand why you were infected. I will talk with you to learn about your potential risk factors for malaria. If a blood sample was not collected at the time of your malaria diagnosis, I will perform a finger prick for blood testing. The questionnaire and blood collection will be performed in your home and will take about 10-15 minutes.

There are minimal risks from participating in the interview. The questionnaire does not ask sensitive questions and measures are in place to keep the information you provide confidential. *If blood collection being performed: One may feel a brief moment of pain when the blood is being collected, but the risk is minimal because the process will be done by a well trained officer.*

As malaria is spread by mosquitoes, your family and neighbours may be at risk for malaria. For this reason, we would like to protect them from contracting malaria and/or treat them if they are already infected. We are currently conducting a study to evaluate community based inteventions and will invite them to participate.

We would like to return in 6-9 months to check on the resolution of your infection. We would also like to return in near the end of the study (expected mid 2017) to check on whether there continues to be malaria in your community. Each of these visits will include blood collection and only take a few minutes. Your participation in these follow-up studies will be voluntary.

The information gathered from this work will be useful for planning future programmes in the fight against malaria. You and your family will be able to receive all benefits or assistance from any future program. If you have any questions, you can contact Mr. Simon Kunene, Program Manager, National Malaria Control Program, Ministry of Health, at 5053804.

Patient Details (data available on immediate notification form, but also confirm with patient)

1. Scan barcode
2. Patient Name _____
3. Date of birth |___|___|/|___|___|/|___|___|
   date month year
4. Gender ☐ Male ☐Female
5. Pregnant ☐ Yes (Trimester_____) ☐ No
6. Inkhundla _____
7. Locality _____
8. Patient contact information
   a. Telephone number 1: _____
   b. Telephone number 2: _____

<u>Case Report</u> (data available on immediate notification form)

9. Date Case Reported |___|___|/|___|___|/|___|___|
   day month year
10. Case Identified by:
    ☐977 Hotline (*If yes*, EPR case ID #_____)

☐Active Case Detection
☐Quality Assurance Program
☐Health facility site visit
☐Phone Call to NMCP
☐Other _____

Presentation at Health Facility (data available from immediate notification form or health facility worker)

11. Health Facility Name ☐ _____ ☐ not applicable
12. Presentation Date ☐|___|___|/|___|___|/|___|___|☐ not applicable
    day month year
13. Disease severity☐ Uncomplicated ☐Severe ☐ Unknown

Diagnosis (data available from health facility worker and/or NMCP)

14. ***Original diagnosis*** confirmed by (may check more than one if applicable)
    ☐ RDT ☐ Microscopy

    If diagnosed by microscopy, specify:
    _____ parasites per microliter (µl)

    Species: ☐*Pf*☐*Pm*☐*Po*☐*Pv*☐Unknown

Second Confirmation of Diagnosis

15. Blood smear taken for second confirmation ☐Yes ☐ No ☐Unknown

    If yes, was blood smear read to confirm diagnosis? ☐ Yes ☐ No ☐Unknown

    Slide read by _____ (slide reader)

    Slide read at _____ (location)

    If yes, what was the slide result?

    ☐ Malaria Parasites Present, specify:
    _____ parasites per microliter (µl)
    Species: ☐*Pf*☐*Pm*☐*Po*☐*Pv*☐Unknown
    ☐ No Malaria Parasites Seen
    ☐ Undetermined
    ☐ Unknown

16. DBS collected ☐Yes ☐ No
    If DBS not collected, why? ☐Patient refused☐Other _____

17. DBS collected from before treatment collected? ☐Yes ☐ No
    If no, why?
    ☐Health facility staff not aware of policy to collect DBS before treatment
    ☐Health facility staff forgot about policy to collect DBS before treatment
    ☐ Sample lost
    ☐ Patient refused
    ☐Other _____

18. If DBS collected as part of QA program, note QAID _____

Investigation Details

19. Investigation date |___|___|/|___|___|/|___|___|
    date month year
20. Conducted at

☐ Homestead of case
☐ Work place of case
☐ Health facility where case presented
☐ Health facility where patient currently admitted
☐ Other_____

21. If investigation not conducted at home, Address
_____
_____
_____
_____

22. Investigation conducted by, (check all that apply)
☐Badelisile☐Calsile☐Gcinumuzi☐Khaya☐Mathokoza☐Mduduzi☐Mpendulo☐Nombuso
☐Nomcebo☐Nomkhosi☐Senzo☐Thulani☐Vusani☐ Other_____

23. GPS coordinates of home (can skip and record later, as interview may not be conducted at subject's home)
S ____° ____' ____"
E ____° ____' ____"

Other Patient Details

24. Nationality
☐ Swaziland
☐ Mozambique
☐ South Africa
☐ Other (specify _____)

25. Occupation
☐ Student
☐ Child or minor but not student
☐Unemployed
☐Farming/Agriculture
☐Manufacturing/Factory
☐Other Manual Labor
☐Small-market sales or trade
☐Office or Clerical Work
☐Other (specify _____)

26. Location of occupation/education
Inkhundla _____
Locality _____
27. Other, specify: _____

Clinical

28. *Ask:* How long were you experiencing symptoms before you sought treatment at the health facility?
____ days

29. *Ask:* Please describe to me the anti-malarial treatment you took. *Check all that apply*
☐Artemether Lumefantrine
☐ Single dose primaquine
☐ Oral Quinine
☐ IV Quinine
☐ IM Quinine
☐Chloroquine

☐ SP/Fansidar
☐ Other (specify _____
☐Unknown

30. Was full course of anti-malarial treatment completed? ☐ Yes ☐ No

31. *Ask:* Have you experienced any side effects? ☐ Yes (specify_____) ☐ No

32. *Ask:* Do you still feel sick? ☐ Yes ☐ No

If no, skip to next question.

If yes, ask: What malaria signs and symptoms still remain?

☐ Fever
☐ Chills
☐ Sweating
☐ Headache
☐ Abdominal Pain
☐ Anemia
☐ Motor weakness
☐ Joint pain
☐ Abdominal Pain
☐ Nausea, Vomiting
☐ Diarrhea
☐ Other (Specify_____)

33. *Ask:* Have you ever previously had malaria? (yes/no)

If no, skip to next question

If yes, ask:

Approximately how many times have you had laboratory confirmed malaria in your life?

_____

- If 1 episode, ask:
  - Approximately how long ago was it that you had malaria? _____ yrs _____ mo
- If >1 episode, ask:
  - Approximately how long ago was the first time you had malaria?
    _____ yrs _____ mos (Enter 0 for years or months if indicated)
  - Approximately how long ago was the most recent time you had malaria?
    _____ yrs _____ mos (Enter 0 for years or months if indicated)

Prior Residence and/or Travel History

34. Have you ever lived or stayed in Mozambique for at least 30 consecutive days?
If yes, approximately how long ago was this visit or stay? _____ yrs _____ mos

35. Have you spent at least one night anywhere else besides your current residence in the past 8 weeks?
☐ Yes ☐ No ☐ Don't know

- ***If no, skip to next question.***
- *If yes, ask:* Where did you sleep overnight, when did you sleep there, why did you sleep there, and personal protection? If slept outside Swaziland, also ask about means of travel and border post of re-entry.

Within Swaziland				
Town / Locality / Tinkhundla	**Duration of Stay**		**Reason for sleeping away from current residence:** -previous residence -business -holiday -visiting friends/family -other (specify, _____)	**Personal protection** -chemoprophylaxis (specify___) -bednet -mosquito repellent or coil -None
	First Night YY/MM/DD	**Last Night YY/MM/DD**		
a.				
b.				
c.				
d.				
e.				

Outside of Swaziland							
Country	**Province / Town**	**Duration of Stay**		**Reason for sleeping away from current residence:** -previous residence -business -holiday -visiting friends/family -other (specify, _____)	**Personal protection** -chemoprophylaxis (specify___) -bednet -mosquito repellent or coil -None	**Means of travel** -Large bus -Kombi (van) -Personal car -Ride share (catch a ride/got a lift) -Airplane -Bicycle -Walked -Other (specify_____)	**Border Post of Re-Entry** - Lavumisa/ Golela - Salitje/ Onverwacht - Mahamba - Gege/ Bothashoop - Sicunusa/ Houtkop - Sandlane/ Nerston - Ngwenya/ Oshoek - Bulembu/ Josefsdal - Matsamo/ Jeppe's Reef - Mananga - Lomahasha/ Namaacha - Mhlumeni/ Goba - Matsapha International Airport - Other
		First Night YY/MM/DD	**Last Night YY/MM/DD**				
a.							
b.							
c.							
d.							
e.							

Household information

36. Including you, how many people live in the household? _____

37. Are you the household head or acting household head? ☐ Yes ☐ No

Vector Control and Personal Protection Measures

38. Have you slept outside in the past week? ☐ Yes ☐ No

39. *Ask:* Do you regularly sleep inside a structure? ☐ Yes ☐ No
    If yes, Ask: Which structure do you regularly sleep in?

40. *Observe:* What are the exterior walls of the house primarily made of?
    ☐ Mud (includes stick and mud)
    ☐Cane, grass, or shrub
    ☐Plywood/wood
    ☐ Cement block or brick
    ☐ No observation conducted

41. *Observe:* What are the interior walls of the house primarily made of?
    ☐ Mud (includes stick and mud)
    ☐Cane, grass, or shrub
    ☐Plywood/wood
    ☐ Cement block or brick
    ☐ Plaster
    ☐ No observation conducted

42. *Observe:* What is the roof primarily comprised of?
    ☐ Grass or palm
    ☐Metal sheets or tile
    ☐ No observation conducted

43. *Observe:* Does the structure where the person sleeps have windows? ☐ Yes ☐ No
    If yes, observe: Are the windows screened or covered? ☐ Yes ☐ No

44. Observe: Are there cracks/spaces at the eaves of the structure? ☐ Yes ☐ No

45. *Ask:* Has this home be sprayed in the past year? ☐ Yes ☐No ☐ Don't Know

    If yes, ask to see spray card to confirm house has been sprayed.
    ☐ Spray card confirmed
    ☐ No spray card
    ☐ Cannot find spray card

    If yes, were all the houses sprayed? ☐ Yes ☐No ☐ Don't Know

    If yes, do you sleep under a sprayed structure? ☐ Yes ☐No ☐ Don't Know

46. *Ask:* Does your household own a bed net? ☐ Yes ☐ No

    If yes, ask: How many bed nets do you have in the household? _____

    How many are treated with insecticide? _____

    Did you sleep under your bed net anytime within the past week? ☐ Yes ☐ No

    If yes, ask: Is your bed net treated with insecticide? ☐ Yes ☐No ☐ Don't Know

    If no, ask: Why didn't you sleep under a bed net within the past week?
    ☐ Too hot

☐ Too cold
☐ Used by someone else
☐ Net not hung up
☐ Net worn out/poor condition
☐ Net dirt
☐ Net bad for health
☐ Don't like shape or color
☐ Other _____

47. Are there any water bodies around or near the house?☐ Yes ☐No ☐ Don't Know

If yes, ask: *what kind of body of water (check all that apply):*

☐river ☐ lake ☐reservoir ☐pond ☐other, specify: _____

If yes, ask: What is the closest distance to a water body?

☐<50m☐ 50-99m☐100-499m ☐500m-999m ☐≥1 km

Thank you for our participation in this study.

48. As mentioned, we would like to return in 6-9 months to check on the resolution of your infection. We would also like to return in mid 2017 to check on whether there continues to be malaria in your community; at this visit we would like to collection in your family and neighbours in addition to you. Each visit will only take a few minutes. Your participation in these follow-up studies will be voluntary. Are you willing to be contacted for these follow-up visits?
☐ Yes ☐ No ☐ Don't Know

49. Case Investigation Comments: Is there any other information that is relevant for this case investigation?
_____
_____
_____
_____
_____
_____

Case Determination *(To be conducted by supervisors following completion of investigation)*

50. Origin of infection
☐Local
☐Imported from another country
☐ Imported from another area of Swaziland
☐ Unknown
☐Other

51. Case epidemiology
☐Index
☐Secondary case from RACD
☐ Secondary case but identified in health facility
☐ Unknown
☐Other

Response Determination *(To be conducted by supervisors following completion of investigation)*

52. Please check all that apply regarding the response:

☐Receptive area –TPE study locality

☐TPE planned
☐TPE not planned as already completed in the past 8 weeks, note aciid: _____ and patient name _____

☐Receptive area: RACD study locality
☐RACD planned
☐RACD not planned as already completed in the past 5 weeks, note aciid: _____ and patient name _____

☐Receptive area: Non-Study locality
☐RACD planned
☐RACD not planned as already completed in the past 5 weeks, note aciid: _____ and patient name _____
☐Imported Network screening planned
☐Other, explain _____

☐Non -receptive area
☐Imported Network screening planned
☐RACD planned, explain why _____
☐Other, explain _____

53. Response comments
_____
_____
_____
_____
_____
_____

54. Determination conducted by_____

Appendix D. Unsuccessful Case Investigation

(Malaria Cases table)

1. Malaria Case ID (Scan Barcode) _____

Investigation Details

2. Investigation date |___|___|/|___|___|/|___|___|
   date month year
3. Investigation conducted by, (check all that apply)
   ☐Calsile ☐Sandile ☐Khaya ☐Mathokoza ☐Mduduzi ☐Mukelwe ☐Nombuso
   ☐Nomcebo ☐Nolwazi ☐Senzo ☐Thulani ☐Fanele ☐ Other_____
4. Conducted at
   - ☐ Homestead of case
   - ☐ Work place of case
   - ☐ Health facility where case presented
   - ☐ Health facility where patient currently admitted
   - ☐ NMCP
   - ☐ Other_____
5. GPS coordinates of home (if subject's home visited)
   Latitude: _____ Longitude: _____

Case Report (data available on immediate notification form)

6. Date Case Reported |___|___|/|___|___|/|___|___|
   date month year
7. Case Identified by:
   - ☐977 Hotline (*If yes*, EPR case ID #_____)
   - ☐Active Case Detection
   - ☐Quality Assurance Program
   - ☐Health facility site visit
   - ☐Phone Call to NMCP
   - ☐Other _____

Presentation at Health Facility (data available from immediate notification form or health facility worker)

8. Health Facility Name ☐ _____ ☐ not applicable
9. Presentation Date ☐ |___|___|/|___|___|/|___|___| ☐ not applicable
   date month year
10. Disease severity ☐ Uncomplicated ☐Severe ☐ Unknown

Patient Details

11. Patient Name: _____
12. Age: ___ years ___ months
13. Gender: ☐Male ☐Female ☐Unknown
14. Contact Number _____
15. Name of household head if any_____
16. Region _____ Inkhundla _____ Locality _____
17. Reason case investigation was unsuccessful, check reason that best describes the situation:
    - ☐Not reported
    - ☐No SMS notification
    - ☐ Contact information is incomplete, inaccurate, not updated
    - ☐ Not reachable by phone
    - ☐ Not able to locate home
    - ☐ Patient is not available (at work, busy etc.)
    - ☐ Patient has left the country
    - ☐ Patient resides here but is currently staying elsewhere (within Swaziland)
    - ☐ Patient has since moved
    - ☐ Refused
    - ☐ Patient died
    - ☐House physically inaccessible
    - ☐Transport limitations

☐Language barrier
☐ Found in ACD and no case investigation completed
☐Other, specify _____

Diagnosis (data available from health facility worker and/or NMCP)

18. ***Original diagnosis*** confirmed by (may check more than one if applicable)
☐ RDT ☐ Microscopy
If diagnosed by microscopy, specify:
_____ parasites per microlitre (µl)
Species: ☐*Pf* ☐*Pm* ☐*Po* ☐*Pv*☐Unknown

Second Confirmation of Diagnosis

19. Blood smear taken for second confirmation ☐Yes ☐ No ☐Unknown
If yes, was blood smear read to confirm diagnosis? ☐ Yes ☐ No ☐Unknown
Slide read by _____(slide reader)
Slide read at _____ (location)
If yes, what was the slide result?
☐ Malaria Parasites Present, specify:
_____ parasites per microlitre (µl)
Species: ☐*Pf* ☐*Pm* ☐*Po* ☐*Pv*☐Unknown
☐ No Malaria Parasites Seen
☐ Undetermined
☐ Unknown

20. DBS collected from patient before treatment? ☐Yes ☐ No
If no, why?
☐Health facility staff not aware of policy to collect DBS before treatment
☐Health facility staff forgot about policy to collect DBS before treatment
☐ Sample lost
☐ Patient refused
☐Other _____
21. If DBS collected as part of QA programme, note QAID _____
22. Comments

_____

_____

_____

_____

23. Directions to homestead:

_____

_____

_____

_____

Case Determination *(based on discussion with family, health facility workers, conducted by CSO or Surveillance Supervisors)*

24. *Presumed origin of infection*
☐Local
☐Imported from another country
☐ Intraported (Imported from another area of Swaziland)
☐ Unknown

25. Date first entered |___|___|/|___|___|/|___|___| Date last modified |___|___|/|___|___|/|___|___|
date month year date month year

Appendix E. (1) Resident Enrollment, Intervention, RACD Arm: Adult Informed Consent Form

Introduction
Greetings! My name is _____. I am conducting surveillance and a research project with the National Malaria Control Program within the Ministry of Health. A member from your household or neighbor had malaria. You may also be at risk for malaria and we would like to invite you to participate in a study where we would implement and evaluate interventions to treat and prevent malaria. Your participation is important, although entirely voluntary. Funding for this study is provided by the Bill & Melinda Gates Foundation.

Why is this study being done?
The purpose of this study is to help Swaziland eliminate malaria. We are evaluating different ways of trying to eliminate malaria. In one group of communities (the first group), everyone will be tested for malaria and only people who have malaria will be referred for treatment. In another group of communities (the second group), everyone will receive treatment and prevention for malaria, whether or not they have malaria. Communities will receive either one of these two interventions. Your community has been selected to test everyone for malaria and treat individuals who are infected (the first group of communities).

How many people will take part in this study?
About 4500 people will be in the first group of communities and 4500 people will be in the second group of communities.

What will happen if I take part in this research study?
Right now, you are only being asked to provide consent for the study activities occurring today. Before you participate in any future visit study activities, we will ask you to provide consent again that day.

Today:
Our study team will ask you a few basic questions about you and your experiences with malaria and will record your answers on a tablet. If you are the head of your household, we will also ask you a few additional questions about how you protect your family against mosquito bites in your home. We will collect your name, address, and contact information so that we can follow up with you in the future. By finger prick, we will collect a small amount of blood (1/20th of a teaspoon) for malaria testing and for research purposes related to malaria. If you are found to be infected with malaria, we will perform a second finger prick to collect a second sample of blood (1/20th of a teaspoon) for research purposes. We will also refer you to the nearest health facility for malaria treatment.

In 6-9 months from today:
If today's test shows that you are infected with malaria, our study team will return to collect a small amount of blood (1/10th of a teaspoon) by finger prick. This will allow us to follow the course of your infection. If today's test shows that you are not infected, we may still return at this time to collect a small blood sample so that we can better understand the body's response to malaria infection.

Near the end of the study:
In order to assess the impact of our study intervention, our study team will return again near the end of the study (mid 2017) to collect an additional small amount of blood (1/20th of a teaspoon) by finger prick from you. We will also ask you a few basic questions about your experiences with malaria and will record your answers on a tablet.

We will perform a rapid test for malaria each time we take a blood sample from you and, if the rapid test shows that you have malaria, we will refer you to the nearest health facility for treatment. We would also like to save a portion of each blood draw for future research studies related to malaria only.

How long will I be in the study?
Today's questionnaire and blood collection will be performed in your home and will take about 10-15 minutes. The future visits for blood collection will occur in your home and take 5-10 minutes.

Can I stop being in the study?
You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. If at any time, you would like to withdraw your information and/or withdraw blood samples from malaria testing, you can contact us. If you choose not to participate in the study or leave the study, there will be no penalty to you or your family. You will not lose any regular benefits and it will not affect your medical care.

What risks can I expect from being in the study?
There are minimal risks from participating in the interview. The questionnaire does not ask sensitive questions and measures are in place to keep the information you provide confidential. You may feel a brief moment of pain when the blood is being collected and there is a small risk of infection at the site of the finger prick, but the risk is minimal because the process will be done by a well-trained officer.

Medical care
We do not expect any problems with participating in the study. Contact our Study Coordinator if you experience a potential side effect from your participation. For urgent and concerning symptoms, such as chest pain, dizziness or feeling faint, having trouble breathing, flushing, or hives (an itchy swollen rash) visit your local health facility or call the national emergency "977 Hotline." If you become ill, you should seek care at your local health facility, where you will be evaluated and treated as indicated for malaria and other illnesses.

Are there benefits to taking part in the study?
If you are found to have malaria on rapid testing today or at future visits, you will benefit from being refered for malaria treatment.

What other choices do I have if I do not take part in the study?
You are free to choose not to participate in the study. If you decide not to take part in the study, there will be no penalty to you. You will still get care from the health facility the way you usually do. Even if you do not take part in the study today, you are still eligible to participate in the follow-up blood test near the end of the study.

How will information about me be kept confidential?

We will not inform anyone of your participation in the study and your name will be kept confidential by replacing it with a number/identifier that will be used throughout the study. There may be situations where we need your name, for example for follow up visits. Therefore, we will keep a key linking your name to your study number/identifier. But only key study staff will have access to this information. All information from the study will be kept in locked cabinets or computers. Organizations that will examine the data are the National Malaria Control Program in Manzini, Swaziland, the Clinton Health Access Initiative in Mbabane, Swaziland and the University of California San Francisco, United States of America. Your name will not appear in any reports or publications.

What are the costs of taking part in this study?
You will not be charged for any of the study procedures.

Will I be paid for taking part in this study?
You will not be paid for taking part in this study.

What are my rights if I take part in this study?
You may choose either to take part or not to take part in the study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you in any way. You will not lose any of your regular benefits, and you can still get your care from your health facility the way you usually do.

Who can I contact in case of injury or if I have future questions about the study?
If you have any questions about this study or your participation, you can contact our Study Coordinator at +268 #### ####. If you were found to have malaria today and experience any adverse health events that may be related to treatment, contact your attending Study Nurse at +268 #### ####. If you wish to voice any problems or concerns you may have about how this study is being conducted, please call the office of the Swaziland Ministry of Health's Ethics Committee at +268 2404 7253.

CONSENT
You have been given a copy of this consent form to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled. If you wish to participate in this study, you should indicate how you would like to participate and sign below.

I agree to be interviewed today. ☐ Yes ☐ No

I agree to provide a blood sample for malaria testing today (by a rapid diagnostic test). ☐ Yes ☐ No

I agree to allow a part my blood sample to be saved for research purposes related to malaria only. ☐ Yes ☐ No

If I am found to be infected with malaria, I agree to provide a second blood sample, which will be saved for research purposes related to malaria only. ☐ Yes ☐ No

Date	Name	Signature or finger print

Date	Name of Person Obtaining Consent	Signature of Person Obtaining Consent

WITNESS (only necessary if consent conducted in language other than English or SiSwati)
I witness that this consent form has been read to the participant in the language recorded below, and the participant has agreed to enroll in the study.
Language that consent was conducted in: _____.

Date	Name	Signature or finger print of witness

Appendix E. (2) Resident Enrollment, Intervention, RACD Arm: Adult Consent & Parent/Guardian Permission Form for Children

(one form per Parent/Guardian: obtains consent from the Parent/Guardian and permission for multiple children)

Introduction

Greetings! My name is _____. I am conducting surveillance and a research project with the National Malaria Control Program within the Ministry of Health. A member from your household or neighbor had malaria. You and your child(ren) may also be at risk for malaria and we would like to invite you and your child(ren) to participate in a study where we would implement and evaluate interventions to treat and prevent malaria. You and your child(ren)'s participation is important, although entirely voluntary. Funding for this study is provided by the Bill & Melinda Gates Foundation.

Why is this study being done?

The purpose of this study is to help Swaziland eliminate malaria. We are evaluating different ways of trying to eliminate malaria. In one group of communities (the first group), everyone will be tested for malaria and only people who have malaria will be referred for treatment. In another group of communities (the second group), everyone will receive treatment and prevention for malaria, whether or not they have malaria. Communities will receive either one of these two interventions. Your community has been selected to test everyone for malaria and treat individuals who are infected (the first group of communities).

How many people will take part in this study?

About 4500 people will be in the first group of communities and 4500 people will be in the second group of communities.

What will happen if we take part in this research study?

Right now, you are only being asked to provide consent for the study activities occurring today. Before you participate in any future visit study activities, we will ask you to provide consent again that day.

Today:

Our study team will ask you a few basic questions about you and your child(ren) and your experiences with malaria and will record your answers on a tablet. We will collect the name(s), address(s), and contact information for you and your child(ren) so that we can follow up with you in the future. By finger prick, I will collect a small amount of blood (1/20th of a teaspoon) from you and your child(ren) for malaria testing and for research purposes related to malaria only. If any of you are found to be infected with malaria, we will perform a second finger prick on the infected individual(s) to collect a second sample of blood (1/20th of a teaspoon) for research purposes. We will also refer infected individual(s) to the nearest health facility for malaria treatment.

In 6-9 months from today:

If today's test shows that you or your child(ren) are infected with malaria, our study team will return to collect a small amount of blood ($1/10^{th}$ of a teaspoon) by finger prick from the infected individual(s). This will allow us to follow the course of your or your child(ren)'s infection. If today's test shows that you and your child(ren) are not infected, we may still return at this time to collect a small blood sample so that we can better understand the body's response to malaria infection.

Near the end of the study:

In order to assess the impact of our study intervention, our study team will return again near the end of the study (mid 2017) to collect an additional small amount of blood (1/20th of a teaspoon) by finger prick from you and your child(ren). We will also ask you a few basic questions about you and your child(ren)'s experiences with malaria and will record your answers on a tablet.

We will perform a rapid test for malaria each time we take a blood sample from you and your child(ren) and, if the rapid test shows that any of you have malaria, we will refer the infected individual(s) to the nearest health facility for treatment. We would also like to save a portion of each blood draw for future research studies related to malaria only.

How long will we be in the study?

Today's questionnaire and blood collection will be performed in your home. The questionnaire will take about 10 minutes and blood collection will take about 5 minutes per person. The future visits for blood collection will occur in your home and take 5-10 minutes per person.

Can we stop being in the study?

You may choose either to have you and your child(ren) take part or not to take part in the study. If you decide to take part in this study, you and/or your child(ren) may leave the study at any time. If at any time, you would like to withdraw your or your child(ren)'s information and/or withdraw blood samples from malaria testing, you can contact us. If you choose not to participate in the study or leave the study, there will be no penalty to you or your family. You and your child(ren) will not lose any regular benefits and it will not affect your or your child(ren)'s medical care.

What risks can we expect from being in the study?

There are minimal risks from participating in the interview. The questionnaire does not ask sensitive questions and measures are in place to keep the information you provide confidential. There may be a brief moment of pain when the blood is being collected and there is a small risk of infection at the site of the finger prick, but the risk is minimal because the process will be done by a well trained officer. Participation or refusal to participate in this study will not affect you or your child(ren)'s care in any way.

Medical care

We do not expect any problems with participating in the study. Contact our Study Coordinator if you or your child(ren) experience a potential side effect from participation. For urgent and concerning symptoms, such as chest pain, dizziness or feeling faint, having trouble breathing, flushing, or hives (an itchy swollen rash), bring your child(ren) to your local health facility or call the national emergency "977 Hotline**."** If you or your child(ren) become ill, go to your local health facility for evaluation and treatment as indicated for malaria and other illnesses.

Are there benefits to taking part in the study?

If you or your child(ren) are found to have malaria on rapid testing today or at future visits, the infected individual(s) will benefit from being refered for malaria treatment.

What other choices do I have if we do not take part in the study?

You are free to choose not to participate in the study. If you decide not to take part in the study, there will be no penalty to you or your child(ren). You all will still get care from the health facility the way you usually do. Even if you and your child(ren) do not take part in the study today, you are all are still eligible to participate in the follow-up blood test near the end of the study.

How will information about us be kept confidential?
We will not inform anyone of you or your child(ren)'s participation in the study and your names will be kept confidential by replacing them with numbers/identifiers that will be used throughout the study. There may be situations where we need your or your child(ren)'s name, for example for follow up visits. Therefore, we will keep a key linking your names to the numbers/identifiers. But only key study staff will have access to this information. All information from the study will be kept in locked cabinets or computers. Organizations that will examine the data are the National Malaria Control Program in Manzini, Swaziland, the Clinton Health Access Initiative in Mbabane, Swaziland and the University of California San Francisco, United States of America. Your names will not appear in any reports or publications.

What are the costs of taking part in this study?
You will not be charged for any of the study procedures.

Will we be paid for taking part in this study?
You will not be paid for taking part in this study.

What are our rights if we take part in this study?
You may choose to have you and your child(ren) either to take part or not to take part in the study. If you decide to take part in the study, you and your child(ren) may leave the study at any time. No matter what decision you make, there will be no penalty in any way. You and your child(ren) will not lose any regular benefits, and you all can still get your care from your health facility the way you usually do.

Who can we contact if we have future questions about the study?
If you have any questions about this study or your participation, you can contact our Study Coordinator at +268 #### ####. If you or your child(ren) were found to have malaria today and experience any adverse health events that may be related to treatment, contact your attending Study Nurse at +268 #### ####. If you wish to voice any problems or concerns you may have about how this study is being conducted, please call the office of the Swaziland Ministry of Health's Ethics Committee at +268 2404 7253.

CONSENT
You have been given a copy of this consent form to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. Your child(ren) are unable to consent for themselves because they are less than 18 years old. By signing this form, you are giving permission for you and your child(ren) or ward(s) to participate in the study. You have the right to decline to participate or to withdraw yourself or your child(ren) at any point in this study without penalty or loss of benefits to which you or your family are otherwise entitled. If you wish to participate in this study, you should indicate how you would like to participate and sign below.

Number of children (<18 years old) that I consent may participate in the study: _____.

I agree to be interviewed today.	☐ Yes	☐ No
I agree to have my child(ren) be interviewed today, if requested by study staff.	☐ Yes	☐ No
I agree to provide a blood sample for malaria testing today (by a rapid diagnostic test).	☐ Yes	☐ No
I agree to have my child(ren) provide blood sample(s) for malaria testing today (by a rapid diagnostic test).	☐ Yes	☐ No
I agree to allow a part of my blood sample to be saved for research purposes related to malaria only.	☐ Yes	☐ No
I agree to allow part of my child(ren)'s blood sample(s) to be saved research purposes related to malaria only.	☐ Yes	☐ No
If I am found to be infected with malaria, I agree to provide a second blood sample, which will be saved for research purposes related to malaria only.	☐ Yes	☐ No
If my child(ren) are found to be infected with malaria, I agree to have all infected child(ren) provide a second blood sample, which will be saved for research purposes related to malaria only.	☐ Yes	☐ No

Date	Name of Parent/Guardian	Signature or fingerprint of Parent/Guardian

Name(s) of children (If indicated, list names of additional children on the back of the form):

Child #1	Child #2	Child #3	Child #4
Child #5	Child #6	Child #7	Child #8

Date	Name of Person Obtaining Consent	Signature of Person Obtaining Consent

WITNESS (only necessary if consent conducted in language other than English or SiSwati)
I witness that this consent form has been read to the participant in the language recorded below, and the participant has agreed to enroll in the study.
Language that consent was conducted in: _____.

Date	Name	Signature or finger print of witness

Appendix E. (3) Resident Enrollment, Intervention, RACD Arm: Minor (12-17yrs) Assent Form

Introduction
Greetings! My name is _____. I am conducting surveillance and a research project with the National Malaria Control Program within the Ministry of Health. A member from your household or neighbor had malaria. You may also be at risk for malaria and we would like to invite you to participate in a study where we would implement and evaluate interventions to treat and prevent malaria. Your parents or guardian have given their permission, but you get to decide if you want to be in this study or not. Your participation is important, although entirely voluntary. Funding for this study is provided by the Bill & Melinda Gates Foundation.

Why is this study being done?
The purpose of this study is to help Swaziland eliminate malaria. We are evaluating different ways of trying to eliminate malaria. In one group of communities (the first group), everyone will be tested for malaria and only people who have malaria will be referred for treatment. In another group of communities (the second group), everyone will receive treatment and prevention for malaria, whether or not they have malaria. Communities will receive either one of these two interventions. Your community has been selected to test everyone for malaria and treat individuals who are infected (the first group of communities).

How many people will take part in this study?
About 4500 people will be in the first group of communities and 4500 people will be in the second group of communities.

What will happen if I take part in this research study?
Right now, you are only being asked to provide assent for the study activities occurring today. Before you participate in any future visit study activities, we will ask you to assent again that day.

Today:
Our study team will ask you and/or your parent or guardian a few basic questions about you and your experiences with malaria and will record your answers on a tablet. We will collect your name, address, and contact information so that we can follow up with you in the future. By finger prick, we will collect a small amount of blood (1/20th of a teaspoon) for malaria testing and for research purposes related to malaria only. If you are found to be infected with malaria, we will perform a second finger prick to collect a second sample of blood (1/20th of a teaspoon) for research purposes. We will also refer you to the nearest health facility for malaria treatment.

In 6-9 months from today:
If today's test shows that you are infected with malaria, our study team will return to collect a small amount of blood (1/10^{th} of a teaspoon) by finger prick. This will allow us to follow the course of your infection. If today's test shows that you are not infected, we may still return at this time to collect a small blood sample so that we can better understand the body's response to malaria infection.

Near the end of the study:
In order to assess the impact of our study intervention, our study team will return again near the end of the study (mid 2017) to collect an additional small amount of blood (1/20th of a teaspoon) by finger prick from you. We will also ask you a few basic questions about your experiences with malaria and will record your answers on a tablet.

We will perform a rapid test for malaria each time we take a blood sample from you and, if the rapid test shows that you have malaria, we will refer you to the nearest health facility for treatment. We would also like to save a portion of each blood draw for future research studies related to malaria only.

How long will I be in the study?
Today's questionnaire and blood collection will be performed in your home and will take about 10-15 minutes. The future visits for blood collection will occur in your home and take 5-10 minutes.

Can I stop being in the study?
With your parent or guardian's permission, you may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. If at any time, you would like to withdraw your information and/or withdraw blood samples from malaria testing, you can have your parent or guardian contact us. If your parent or guardian wants you to withdraw from the study, you must withdraw. If you choose not to participate in the study or leave the study, there will be no penalty to you or your family. You will not lose any regular benefits and it will not affect your medical care.

What risks can I expect from being in the study?
There are minimal risks from participating in the interview. The questionnaire does not ask sensitive questions and measures are in place to keep the information you provide confidential. You may feel a brief moment of pain when the blood is being collected and there is a small risk of infection at the site of the finger prick, but the risk is minimal because the process will be done by a well trained officer. Participation or refusal to participate in this study will not affect your care in any way.

Medical care
We do not expect any problems with participating in the study. Have your parent/guardian contact our Study Coordinator if you experience a potential side effect. For urgent and concerning symptoms, such as chest pain, dizziness or feeling faint, having trouble breathing, flushing, or hives (an itchy swollen rash), have your parent/guardian bring you to your local health facility or call the national emergency "977 Hotline." If you become ill, you should seek care at your local health facility, where you will be evaluated and treated as indicated for malaria and other illnesses.

What other choices do I have if I do not take part in the study?
You are free to choose not to participate in the study. If you decide not to take part in the study, there will be no penalty to you. You will still get care from the health facility the way you usually do. Even if you do not take part in the study today, you are still eligible to participate in the follow-up blood test near the end of the study.

Are there benefits to taking part in the study?
If you are found to have malaria on rapid testing today or at future visits, you will benefit from being refered for malaria treatment.

How will information about me be kept confidential?
We will not inform anyone of your participation in the study and your name will be kept confidential by replacing it with a number/identifier that will be used throughout the study. There may be situations where we need your name, for example for follow up visits. Therefore, we will keep a key linking your name to your study number/identifier. But only key study staff will have access to this information. All information from the study will be kept in locked cabinets or computers. Organizations that will examine the data are the National Malaria Control Program in Manzini, Swaziland, the Clinton Health Access Initiative in Mbabane, Swaziland and the University of California San Francisco, United States of America. Your name will not appear in any reports or publications.

What are the costs of taking part in this study?
You will not be charged for any of the study procedures.

Will I be paid for taking part in this study?
You will not be paid for taking part in this study.

What are my rights if I take part in this study?
With your parent or guardian's permission, you may choose either to take part or not to take part in the study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you in any way. You will not lose any of your regular benefits, and you can still get your care from your health facility the way you usually do.

Who can I contact if I am injured or I have future questions about the study?
If you have any questions about this study or your participation, you can have your parent/guardian contact our Study Coordinator at +268 #### ####. If you were found to have malaria today and experience any adverse health events that may be related to treatment, have your parent/guardian contact your attending Study Nurse at +268 #### ####. If you wish to voice any problems or concerns you may have about how this study is being conducted, please have your parent/guardian call the office of the Swaziland Ministry of Health's Ethics Committee at +268 2404 7253.

ASSENT
You have been given a copy of this assent form to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled. If you wish to participate in this study, you should indicate how you would like to participate and sign below.

This study was explained to me clearly.	☐ Yes	☐ No
I agree to be interviewed today.	☐ Yes	☐ No
I agree to provide a blood sample for malaria testing today (by a rapid diagnostic test).	☐ Yes	☐ No
I agree to allow a part of my blood sample to be saved for research purposes related to malaria only.	☐ Yes	☐ No
If I am found to be infected with malaria, I agree to provide a second blood sample, which will be saved for research purposes related to malaria only.	☐ Yes	☐ No

Date	Name of Minor	Signature or finger print of Minor

Date	Name of Person Obtaining Consent	Signature of Person Obtaining Consent

WITNESS (only necessary if assent conducted in language other than English or SiSwati)
I witness that this assent form has been read to the participant in the language recorded below, and the participant has agreed to enroll in the study.
Language that assent was conducted in:_____.

Date	Name	Signature or finger print of witness

Appendix F. (1) Resident Enrollment, Intervention, TPE Arm: Adult Informed Consent Form

Introduction
Greetings! My name is _____. I am conducting surveillance and a research project with the National Malaria Control Program within the Ministry of Health. A member from your household or neighbor had malaria. You may also be at risk for malaria and we would like to invite you to participate in a study where we would implement and evaluate interventions to treat and prevent malaria. Your participation is important, although entirely voluntary. Funding for this study is provided by the Bill & Melinda Gates Foundation.

Why is this study being done?
The purpose of this study is to help Swaziland eliminate malaria. We are evaluating different ways of trying to eliminate malaria. In one group of communities (the first group), everyone will be tested for malaria and only people who have malaria will be referred for treatment. In another group of communities (the second group), everyone will receive treatment and prevention for malaria, whether or not they have malaria. Communities will receive either one of these two interventions. Your community has been selected to give everyone medication for treatment and prevention of malaria without testing for infection (the second group of communities).

How many people will take part in this study?
About 4500 people will be in the first group of communities and 4500 people will be in the second group of communities.

What will happen if I take part in this research study?
Right now, you are being asked to provide consent for the study activities occurring today and for a return visit in 7-10 days. Before you participate in any future visit study activities, we will ask you to provide consent again that day.

Today:

Our study team will ask you a few basic questions about you and your experiences with malaria and record your answers on a tablet. If you are the head of your household, we will also ask you a few additional questions about how you protect your family against mosquito bites in your home. We will collect your name, address, and contact information so that we can follow up with you in the future. We will also ask you a few questions about your and your family's medical history and use of medications to see if it is safe for you to be given a malaria medicine called dihydroartemisinin-piperaquine, also called DP for short.

If it is safe for you to be given DP, our study team will explain to you how to take this medication. Each daily dose consists of 3 pills that should be taken together. You will take the first dose of a 3-day course of DP today. We will leave you with the second and third doses, which should be taken approximately the same time tomorrow and the day after, respectively. If a dose is missed, it should be taken as soon as possible. But do not take more than 1 dose of DP each day. You will not be given DP if it is unsafe for you. Everyone in your community is being given 3 days of DP to treat malaria, whether or not they have it. DP is useful for treatment of malaria, and may also prevent malaria infection in the near future.

If it is not safe for you to be given DP, we will collect a small amount of blood (1/20th of a teaspoon) for malaria testing and for research purposes related to malaria only by finger prick. If you are found to be infected with malaria, we will perform a second finger prick to collect a second sample of blood (1/20th of a teaspoon) for research purposes. We will also refer you to the nearest health facility for malaria treatment with a medication that is safe for you.

In 7-10 days from today:

We may return to perform a pill count. Therefore, please keep your medicine packaging for at least 10 days. Additionally, we may invite you to participate in a group discussion about your experience with the intervention.

Near the end of the study:

In order to assess the impact of our study intervention, our study team will return again near the end of the study (mid 2017) to collect a small amount of blood (1/20th of a teaspoon) by finger prick from you. We will also ask you a few basic questions about your experiences with malaria and will record your answers on a tablet. We will perform a rapid test for malaria and, if the rapid test shows that you have malaria, we will refer you to the nearest health facility for treatment. We would also like to save a portion of this blood draw for future research studies related to malaria only.

How long will I be in the study?
Today's questionnaire and administration of malaria medicine will be performed in your home and will take about 10-15 minutes. The future visits for pill counts and blood collection will occur in your home and take 5-10 minutes. If you are selected, the group discussion 7-10 days from today will take an hour.

Can I stop being in the study?
You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. If you experience symptoms related to taking DP, it is safe to stop taking DP before completing your pills. If at any time, you would like to withdraw your information and/or withdraw blood samples from malaria testing, you can contact us. If you choose not to participate in the study or leave the study, there will be no penalty to you or your family. You will not lose any regular benefits and it will not affect your medical care. The study doctor may also stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What risks can I expect from being in the study?
There are minimal risks from participating in the interview. The questionnaire does not ask sensitive questions and measures are in place to keep the information you provide confidential. You may feel a brief moment of pain when the blood is being collected and there is a small risk of infection at the site of the finger prick, but the risk is minimal because the process will be done by a well trained officer.

DP has been shown to be safe and very effective for treatment and prevention of malaria in all ages, including children. Serious health problems have rarely been reported. There may be some side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study. If you do experience side effects, please ask your rural health motivator to contact study

staff or you may contact study staff directly. For urgent issues, you should stop taking DP, call our study staff, and seek care at a local health facility. The risks and side effects related to the study medication, DP, include those which are:

- **Likely:** No side effect is likely, but the most common is cough or fever
- **Less Likely:** low red blood cells**,** headache, lack of energy, vomiting, diarrhea, abdominal pain
- **Rare but serious: itching, inflammation or enlargement of the liver, heart rhythm problems**

Medical care.
We do not expect any problems with participating in the study. While DP is safe and not expected to cause any side effects, contact your attending Study Nurse if you experience a potential side effect. For urgent and concerning symptoms, such as chest pain, dizziness or feeling faint, having trouble breathing, flushing, or hives (an itchy swollen rash), visit your local health facility or call the national emergency "977 Hotline." Even if it is not safe for you to be given the DP medicine, this does not mean that you cannot be treated for malaria with other medication. Therefore, if you think you have malaria, or are ill, you should still go to the health care clinic.

Are there benefits to taking part in the study?
The medication we will give you today will treat malaria if you are infected and it may prevent future infection. If you are found to have malaria by rapid testing at future visits, you will benefit from being referred for malaria treatment. DP is NOT a substitute for medicine to prevent malaria when traveling to areas where you will be at high risk of malaria infection. If you are traveling, please visit your health facility to assess your risk and if you should take medicine to prevent malaria during your trip.

What other choices do I have if I do not take part in the study?
You are free to choose not to participate in the study. If you decide not to take part in the study, there will be no penalty to you. You will still get care from the health facility the way you usually do. Similarly, if you do not qualify for malaria medicine, and you become ill, you can still get care from the health facility and be evaluated and treated as indicated for malaria and other illnesses. Even if you do not take part in the study today, you are still eligible to participate in the follow-up blood test near the end of the study.

How will information about me be kept confidential?
We will not inform anyone of your participation in the study and your name will be kept confidential by replacing it with a number/identifier that will be used throughout the study. There may be situations where we need your name, for example for follow up visits. Therefore, we will keep a key linking your name to your study number/identifier. But only key study staff will have access to this information. All information from the study will be kept in locked cabinets or computers. Organizations that will examine the data are the National Malaria Control Program in Manzini, Swaziland, the Clinton Health Access Initiative in Mbabane, Swaziland and the University of California San Francisco, United States of America. Your name will not appear in any reports or publications.

What are the costs of taking part in this study?
You will not be charged for any of the study procedures or medications.

Will I be paid for taking part in this study?
You will not be paid for taking part in this study.

What are my rights if I take part in this study?
You may choose either to take part or not to take part in the study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you in any way. You will not lose any of your regular benefits, and you can still get your care from your health facility the way you usually do.

Who can I contact in case of injury or if I have future questions about the study?
If you have any questions about this study or your participation, you can contact our Study Coordinator at +268 #### ####. If you have experienced any adverse health events that may be related to DP, please contact your attending Study Nurse at +268 #### ####. If you wish to voice any problems or concerns you may have about how this study is being conducted, please call the office of the Swaziland Ministry of Health's Ethics Committee at +268 2404 7253.

CONSENT
You have been given a copy of this consent form to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled. If you wish to participate in this study, you should indicate how you would like to participate and sign below.

I agree to be interviewed today.	☐ Yes	☐ No
I agree to take anti-malarial medication, if eligible.	☐ Yes	☐ No
I agree to a possible pill count and group discussion in 7-10 days.	☐ Yes	☐ No
If I am not eligible to receive DP, I agree to provide a blood sample for malaria testing today (by a rapid diagnostic test).	☐ Yes	☐ No
If I am not eligible to receive DP, I agree to allow a part of my blood sample to be saved for research purposes related to malaria only).	☐ Yes	☐ No
If I am not eligible to DP and I am found to be infected with malaria, I agree to provide a second blood sample, which will be saved for research purposes related to malaria only.	☐ Yes	☐ No

Date	Name	Signature or finger print

Date	Name of Person Obtaining Consent	Signature of Person Obtaining Consent

WITNESS (only necessary if consent conducted in language other than English or SiSwati)
I witness that this consent form has been read to the participant in the language recorded below, and the participant has agreed to enroll in the study.
Language that consent was conducted in:_____.

Date	Name	Signature or finger print of witness

Appendix F. (2) Resident Enrollment, Intervention, TPE Arm: Adult Consent & Parent/Guardian Permission Form for Children

(one form per Parent/Guardian: obtains consent from the Parent/Guardian and permission for multiple children)

Introduction

Greetings! My name is _____. I am conducting surveillance and a research project with the National Malaria Control Program within the Ministry of Health. A member from your household or neighbor had malaria. You and your child(ren) may also be at risk for malaria and we would like to invite you and your child(ren) to participate in a study where we would implement and evaluate interventions to treat and prevent malaria. You and your child(ren)'s participation is important, although entirely voluntary. Funding for this study is provided by the Bill & Melinda Gates Foundation.

Why is this study being done?

The purpose of this study is to help Swaziland eliminate malaria. We are evaluating different ways of trying to eliminate malaria. In one group of communities (the first group), everyone will be tested for malaria and only people who have malaria will be referred for treatment. In another group of communities (the second group), everyone will receive treatment and prevention for malaria, whether or not they have malaria. Communities will receive either one of these two interventions. Your community has been selected to give everyone medication for treatment and prevention of malaria without testing for infection (the second group of communities).

How many people will take part in this study?

About 4500 people will be in the first group of communities and 4500 people will be in the second group of communities.

What will happen if we take part in this research study?

Right now, you are being asked to provide consent for the study activities occurring today and for a return visit in 7-10 days. Before you or your child(ren) participate in any future visit study activities, we will ask you to provide consent again that day.

Today:

Our study team will ask you a few basic questions about you and your child(ren) and your experiences with malaria and record your answers on a tablet. We will collect the names, addresses, and contact information for you and your child(ren) so that we can follow up with you in the future. We will also ask you a few questions about you, your child(ren)'s and your family's medical history and use of medications to see if it is safe for you and your child(ren) to be given a malaria medicine called dihydroartemisinin-piperaquine, also called DP for short.

For individual(s) who can safely be given DP, our study team will explain to you how to take this medication and give this medication to your child(ren). You will be given an adult dose of DP. Your child(ren) will be weighed, and the appropriate weight-based dose will be given for each child. All pills for each daily dose should be taken together. You and your child(ren) will be given the first dose of a 3-day course of DP today. We will leave you with the second and third doses, which should be taken at approximately the same time tomorrow and the day after, respectively. If a dose is missed, it should be taken as soon as possible. But do not take more than 1 dose of DP each day. You and your child(ren) will not be given DP if it is unsafe. Everyone in your community is being given 3 days of DP to treat malaria, whether or not they have it. DP is useful for treatment of malaria, and may also prevent malaria infection in the near future.

If it is not safe for you or your child(ren) to be given DP, we will collect a small amount of blood (1/20th of a teaspoon) for malaria testing and for research purposes related to malaria only by finger prick. If you or your child(ren) are found to be infected with malaria, we will perform a second finger prick on the infected individual(s) to collect a second sample of blood (1/20th of a teaspoon) for research purposes. We will also refer the infected individual(s) to the nearest health facility for malaria treatment with a medication that is safe for you and/or your child(ren).

In 7-10 days from today:

We may return to perform a pill count. Therefore, please keep all medicine packaging for at least 10 days. Additionally, we may invite you to participate in a group discussion about your experience with the intervention.

Near the end of the study:

In order to assess the impact of our study intervention, our study team will return again near the end of the study (mid 2017) to collect a small amount of blood (1/20th of a teaspoon) by finger prick from you and your child(ren). We will also ask you a few basic questions about you and your child(ren)'s experiences with malaria and will record your answers on a tablet. We will perform a rapid test for malaria on you and your child(ren) and, if the rapid test shows that any of you have malaria, we will refer the infected individual(s) to the nearest health facility for treatment. We would also like to save a portion of these blood draws for future research studies related to malaria only.

How long will we be in the study?

Today's questionnaire and administration of malaria medicine will be performed in your home and will take about 10-15 minutes. The future visits for pill counts and blood collection will occur in your home and take 5-10 minutes per person. If you or your child(ren) are selected, the group discussion in 7-10 days from today will take an hour.

Can we stop being in the study?

You may choose either have you and your child take part or not take part in the study. If you decide to take part in this study, you or your child(ren) may leave the study at any time. If you or your child(ren) experience symptoms related to taking DP, it is safe for that individual to stop taking DP before completing the pills. If at any time you would like to withdraw your or your child(ren)'s information and/or withdraw blood samples from malaria testing, you can contact us. If you choose not to participate in the study or leave the study, there will be no penalty to you or your family. You and your child(ren) will not lose any regular benefits and it will not affect your or your child(ren)'s medical care. The study doctor may also stop you or your child(ren) from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What risks can we expect from being in the study?

There are minimal risks from participating in the interview. The questionnaire does not ask sensitive questions and measures are in place to keep the information you provide confidential. There may be a brief moment of pain when the blood is being collected and there is a small risk of infection at the site of the finger prick, but the risk is minimal because the process will be done by a well trained officer.

DP has been shown to be safe and very effective for treatment and prevention of malaria in all ages, including children. Serious health problems have rarely been reported. There may be some side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about your or your child(ren)'s participation in the study. If you or your child(ren) experience side effects, please ask your rural health motivator to contact study staff or you may contact study staff directly. For urgent issues, you or your child(ren) should stop taking DP and be brought for care at a local health facility and you should call our study staff. The risks and side effects related to the study medication, DP, include those which are:

- **Likely:** No side effect is likely, but the most common is cough or fever
- **Less Likely:** low red blood cells**,** headache, lack of energy, vomiting, diarrhea, abdominal pain
- **Rare but serious: itching, inflammation or enlargement of the liver, heart rhythm problems**

Medical care

We do not expect any problems with participating in the study. While DP is safe and not expected to cause any side effects, contact your attending Study Nurse if you or your child(ren) experiences a potential side effect. For urgent and concerning symptoms, such as chest pain, dizziness or feeling faint, having trouble breathing, flushing, or hives (an itchy swollen rash), seek care at your local health facility or call the national emergency "977 Hotline." Even if it is not safe for you or your child(ren) to be given the DP medicine, this does not mean that you cannot be treated for malaria with other medication. Therefore, if you think you or your child(ren) have malaria, or are ill, you should still go to the health care clinic.

Are there benefits to taking part in the study?

The medication you and your child(ren) will be given today will treat malaria if you are infected and it may prevent future infection. DP is NOT a substitute for medicine to prevent malaria when traveling to areas where you will be at high risk of malaria infection. If you or your child(ren) are traveling, please visit your health facility to assess your risk and see if you or your child(ren) should take medicine to prevent malaria during your trip.

What other choices are there if we do not take part in the study?

If you decide not to take part in the study, there will be no penalty. You and your child(ren) will still get care from the health facility the way you usually do. Similarly, if you or your child(ren) do not qualify for malaria medicine, and become ill, you can still get care from the health facility and be evaluated and treated as indicated for malaria and other illnesses. Even if you or your child(ren) do not take part in the study today, you are all still eligible to participate in the follow-up blood test near the end of the study.

How will information about us be kept confidential?

We will not inform anyone of your or your child(ren)'s participation in the study and your names(s) will be kept confidential by replacing them with numbers/identifiers that will be used throughout the study. There may be situations where we need your or your child(ren)'s name, for example for follow up visits. Therefore, we will keep a key linking your names to your study numbers/identifiers. But only key study staff will have access to this information. All information from the study will be kept in locked cabinets or computers. Organizations that will examine the data are the National Malaria Control Program in Manzini, Swaziland, the Clinton Health Access Initiative in Mbabane, Swaziland and the University of California San Francisco, United States of America. Your and your child(ren)'s names will not appear in any reports or publications.

What are the costs of taking part in this study?

You will not be charged for any of the study procedures or medications.

Will we be paid for taking part in this study?

You will not be paid for taking part in this study.

What are our rights if we take part in this study?

You may choose to have you and your child(ren) either to take part or not to take part in the study. If you decide to take part in the study, you and your child(ren) may leave the study at any time. No matter what decision you make, there will be no penalty in any way. You and your child(ren) will not lose any regular benefits, and you all can still get your care from your health facility the way you usually do.

Who can we contact if we have future questions about the study?

If you have any questions about this study or your participation, you can contact our Study Coordinator at +268 #### ####. If you or your child(ren) child experienced any adverse health events that may be related to DP, contact your attending Study Nurse at +268 #### ####. If you wish to voice any problems or concerns you may have about how this study is being conducted, please call the office of the Swaziland Ministry of Health's Ethics Committee at +268 2404 7253.

CONSENT

You have been given a copy of this consent form to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. Your child(ren) are unable to consent for themselves because they are less than 18 years old. By signing this form, you are giving permission for you and your child(ren) or ward(s) to participate in the study. You have the right to decline to participate or to withdraw yourself or your child(ren) at any point in this study without penalty or loss of benefits to which you or your family are otherwise entitled. If you wish to participate in this study, you should indicate how you would like to participate and sign below.

Number of children (<18 years old) that I consent may participate in the study: _____.

I agree to be interviewed today.	☐ Yes	☐ No
I agree have my child(ren) be interviewed today, if requested by study staff.	☐ Yes	☐ No
I agree to take antimalarial medication, if eligible.	☐ Yes	☐ No
I agree to have my child(ren) take antimalarial medication, if eligible.	☐ Yes	☐ No
I agree to a possible pill count and group discussion in 7-10 days.	☐ Yes	☐ No
If I am not eligible to receive DP, I agree to provide a blood sample for malaria testing today (by a rapid diagnostic test).	☐ Yes	☐ No

If my child(ren) are not eligible to receive DP, I agree to have them provide blood sample(s) for malaria testing today (by a rapid diagnostic test). ☐ Yes ☐ No

If I am not eligible to receive DP, I agree to allow a part of my blood sample to be saved for research purposes related to malaria only). ☐ Yes ☐ No

If my child(ren) are not eligible to receive DP, I agree to allow a part of their blood sample(s) to be saved for research purposes related to malaria only). ☐ Yes ☐ No

If I am not eligible to receive DP and I am found to be infected with malaria, I agree to provide a second Blood sample, which will be saved for research purposes related to malaria only. ☐ Yes ☐ No

If my child(ren) are not eligible to receive DP and they are found to be infected with malaria, I agree to provide a second blood sample, which will be saved for research purposes related to malaria only. ☐ Yes ☐ No

Date	Name of Parent/Guardian	Signature or fingerprint of Parent/Guardian

Name(s) of children (If indicated, list names of additional children on the back of the form):

Child #1	Child #2	Child #3	Child #4
Child #5	Child #6	Child #7	Child #8

Date	Name of Person Obtaining Consent	Signature of Person Obtaining Consent

WITNESS (only necessary if consent conducted in language other than English or SiSwati)
I witness that this consent form has been read to the participant in the language recorded below, and the participant has agreed to enroll in the study.
Language that consent was conducted in:_____.

Date	Name	Signature or finger print of witness

Information to help parent/guardian keep track of dosing regimen for all of their child(ren):

Illiterate mothers can be assisted by any family member who can read during administration of the drugs. Different color coded stickers will be used for different children of different weight/age groups.

If no family member is capable of providing assistance for keeping track of the drug doses for different children, it will be the responsibility of the study nurse to revisit the family to administer the drugs. Families provided 3 day DOT by a study nurse due to illiteracy will be excluded from the measurement of adherence.

Weight band	Regimen	Number of days	Number of pills each day	Packaging
<7kg	Not eligible			
7-12 kg	320mg /40mg	3	½	Pink Bottle
13-23 kg	320mg /40mg	3	1	Green box
24-35 kg	320mg /40mg	3	2	Orange box
36-74 kg	320mg /40mg	3	3	Purple box
> 74 kg	320mg /40mg	3	4	Blue bag

	Child's name	Eligible for DP?	Weight	Number of days	Number of pills each day	Packaging
1				3		
2				3		
3				3		
4				3		
5				3		
6				3		
7				3		
8				3		
9				3		
10				3		
11				3		
12				3		
13				3		
14				3		
15				3		
16				3		
17				3		
18				3		
19				3		
20				3		

Appendix F. (3) Resident Enrollment, Intervention, TPE Arm: Minor (12-17yrs) Assent Form

Introduction

Greetings! My name is _____. I am conducting surveillance and a research project with the National Malaria Control Program within the Ministry of Health. A member from your household or neighbor had malaria. You may also be at risk for malaria and we would like to invite you to participate in a study where we would implement and evaluate interventions to treat and prevent malaria. Your participation is important, although entirely voluntary. Funding for this study is provided by the Bill & Melinda Gates Foundation.

Why is this study being done?

The purpose of this study is to help Swaziland eliminate malaria. We are evaluating different ways of trying to eliminate malaria. In one group of communities (the first group), everyone will be tested for malaria and only people who have malaria will be referred for treatment. In another group of communities (the second group), everyone will receive treatment and prevention for malaria, whether or not they have malaria. Communities will receive either one of these two interventions. Your community has been selected to give everyone medication for treatment and prevention of malaria without testing for infection (the second group of communities).

How many people will take part in this study?

About 4500 people will be in the first group of communities and 4500 people will be in the second group of communities.

What will happen if I take part in this research study?

Right now, you are being asked to provide assent for the study activities occurring today and for a return visit in 7-10 days. Before you participate in any future visit study activities, we will ask you to provide assent again that day.

Today:

Our study team will ask you a few basic questions about you and your experiences with malaria and record your answers on a tablet. We will collect your name, address, and contact information so that we can follow up with you in the future. We will also ask you a few questions about your and your family's medical history and use of medications to see if it is safe for you to be given a malaria medicine called dihydroartemisinin-piperaquine, also called DP for short.

If it is safe for you to be given DP, our study team will explain to your parent or guardian how you should take this medication. You will be weighed, and will be given an appropriate weight-based dose of DP. All pills for each daily dose should be taken together. You will be given the first weight-based dose of a 3-day course of DP today. We will leave the second and third doses with your parent or guardian, which should be taken approximately the same time tomorrow and the day after, respectively. If a dose is missed, it should be taken as soon as possible. But do not take more than 1 dose of DP each day. You will not be given DP if it is unsafe for you. Everyone in your community is being given 3 days of DP to treat malaria, whether or not they have it. DP is useful for treatment of malaria, and may also prevent malaria infection in the near future.

If it is not safe for you to be given DP, we will collect a small amount of blood (1/20th of a teaspoon) for malaria testing and for research purposes related to malaria only by finger prick. If you are found to be infected with malaria, we will perform a second finger prick to collect a second sample of blood (1/20th of a teaspoon) for research purposes. We will also refer you to the nearest health facility for malaria treatment with a medication that is safe for you.

In 7-10 days from today:

We may return to perform a pill count. Therefore, please have your parent or guardian keep your medicine packaging for at least 10 days.

Near the end of the study:

In order to assess the impact of our study intervention, our study team will return again near the end of the study (mid 2017) to collect a small amount of blood (1/20th of a teaspoon) by finger prick from you. We will also ask you a few basic questions about your experiences with malaria and will record your answers on a tablet. We will perform a rapid test for malaria and, if the rapid test shows that you have malaria, we will refer you to the nearest health facility for treatment. We would also like to save a portion of this blood draw for future research studies related to malaria only.

How long will I be in the study?

Today's questionnaire and administration of malaria medicine will be performed in your home and will take about 10-15 minutes. The future visits for pill counts and blood collection will occur in your home and take 5-10 minutes. If you are selected, the group discussion 7-10 days from today will take an hour.

Can I stop being in the study?

With your parent or guardian's permission, you may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. If you experience symptoms related to taking DP, it is safe to stop taking DP before completing your pills. If at any time, you would like to withdraw your information and/or withdraw blood samples from malaria testing, you can have your parent or guardian contact us. If your parent or guardian wants you to withdraw from the study, you must withdraw. If you choose not to participate in the study or leave the study, there will be no penalty to you or your family. You will not lose any regular benefits and it will not affect your medical care. The study doctor may also stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What risks can I expect from being in the study?

There are minimal risks from participating in the interview. The questionnaire does not ask sensitive questions and measures are in place to keep the information you provide confidential. You may feel a brief moment of pain when the blood is being collected and there is a small risk of infection at the site of the finger prick, but the risk is minimal because the process will be done by a well trained officer.

DP has been shown to be safe and very effective for treatment and prevention of malaria in all ages, including children. Serious health problems have rarely been reported. There may be some side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study. If you do experience side effects, please ask your rural health motivator to contact study staff or you may contact study staff directly. For urgent issues, you should stop taking DP and have your parent or guardian contact our study staff and bring you for care at a local health facility. The risks and side effects related to the study medication, DP, include those which are:

- **Likely:** No side effect is likely, but the most common is cough or fever
- **Less Likely:** low red blood cells**,** headache, lack of energy, vomiting, diarrhea, abdominal pain
- **Rare but serious: itching, inflammation or enlargement of the liver, heart rhythm problems**

Medical care.
We do not expect any problems with participating in the study. While DP is safe and not expected to cause any side effects, have your parent/guardian contact your attending Study Nurse if you experience a potential side effect. For urgent and concerning symptoms, such as chest pain, dizziness or feeling faint, having trouble breathing, flushing, or hives (an itchy swollen rash), have your parent/guardian bring you to your local health facility or call the national emergency "977 Hotline." Even if it is not safe for you to be given the DP medicine, this does not mean that you cannot be treated for malaria with other medication. Therefore, if you think you have malaria, or are ill, you should still go to the health care clinic.

Are there benefits to taking part in the study?
The medication we will give you today will treat malaria if you are infected and it may prevent future infection. If you are found to have malaria by rapid testing future visits, you will benefit from being referred for malaria treatment. DP is NOT a substitute for medicine to prevent malaria when traveling to areas where you will be at high risk of malaria infection. If you are traveling, please visit your health facility to assess your risk and see if you should take medicine to prevent malaria during your trip.

What other choices do I have if I do not take part in the study?
You are free to choose not to participate in the study. If you decide not to take part in the study, there will be no penalty to you. You will still get care from the health facility the way you usually do. Similarly, if you do not qualify for malaria medicine, and you become ill, you can still get care from the health facility and be evaluated and treated as indicated for malaria and other illnesses. Even if you do not take part in the study today, you are still eligible to participate in the follow-up blood test near the end of the study.

How will information about me be kept confidential?
We will not inform anyone of your participation in the study and your name will be kept confidential by replacing it with a number/identifier that will be used throughout the study. There may be situations where we need your name, for example for follow up visits. Therefore, we will keep a key linking your name to your study number/identifier. But only key study staff will have access to this information. All information from the study will be kept in locked cabinets or computers. Organizations that will examine the data are the National Malaria Control Program in Manzini, Swaziland, the Clinton Health Access Initiative in Mbabane, Swaziland and the University of California San Francisco, United States of America. Your name will not appear in any reports or publications.

What are the costs of taking part in this study?
You will not be charged for any of the study procedures.

Will I be paid for taking part in this study?
You will not be paid for taking part in this study.

What are my rights if I take part in this study?
With your parent or guardian's permission, you may choose either to take part or not to take part in the study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you in any way. You will not lose any of your regular benefits, and you can still get your care from your health facility the way you usually do.

Who can I contact in case of injury or if I have future questions about the study?
If you have any questions about this study or your participation, you can have your parent/guardian contact our Study Coordinator at +268 #### ####. If you have experienced any adverse health events that may be related to DP, please have your parent/guardian contact your attending Study Nurse at +268 #### ####. If you wish to voice any problems or concerns you may have about how this study is being conducted, please have your parent/guardian call the office of the Swaziland Ministry of Health's Ethics Committee at +268 2404 7253.

ASSENT
You have been given a copy of this assent form to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled. If you wish to participate in this study, you should indicate how you would like to participate and sign below.

This study was explained to me clearly.	☐ Yes	☐ No
I agree to be interviewed today.	☐ Yes	☐ No
I agree to take antimalarial medication, if elegible.	☐ Yes	☐ No
I agree to a possible pill count and group discussion in 7-10 days.	☐ Yes	☐ No
If I am not eligible to receive DP, I agree to provide a blood sample for malaria testing today (by a rapid diagnostic test).	☐ Yes	☐ No
If I am not eligible to receive DP, I agree to allow a part of my blood sample to be saved for research purposes related to malaria only).	☐ Yes	☐ No
If I am not eligible to receive DP and I am found to be infected with malaria, I agree to provide a second blood sample, which will be saved for research purposes related to malaria only.	☐ Yes	☐ No

Date	Name of Minor	Signature or fingerprint of Minor
Date	Name of Person Obtaining Consent	Signature of Person Obtaining Consent

WITNESS (only necessary if assent conducted in language other than English or SiSwati)
I witness that this assent form has been read to the participant in the language recorded below, and the participant has agreed to enroll in the study.
Language that assent was conducted in:_____.

Date	Name	Signature or finger print of witness

Quiz to assess participant's understanding of the study (to be given at time of TPE intervention visit only)

If the participant does not answer at least 4 out of the 5 questions correctly, the study team should reread the consent form and reassess the participant's understanding again. The study team should ensure that the participant is able to answer question 3 correctly, and re-explain how DP should be taken and given to child(ren).

1. Is participation in this study voluntary?

2. How should you take the malaria medication (DP) / How should you give the malaria medication (DP) to your child(ren)?

Appendix G: Neighborhood Information

Index case ID (aciid): _____

Neighborhood ID: _____

(NOTE This is a unique ID automatically generated by the tablet. If the same neighborhood has multiple interventions at different time points, it will receive a neighborhood ID with each episode)

Response determination:

☐Study area- RACD
☐Study area – TPE
☐Non study area- RACD

Visit 1: Date and Time of arrival

Date: _____ (dd/mm/yyyy)
Time of arrival: ____: _____ (hh:mm)
Time of departure: ____: _____ (hh:mm)
Result code: _____

Visit 2: Date and Time of arrival

Date: _____ (dd/mm/yyyy)
Time of arrival: ____: _____ (hh:mm)
Time of departure: ____: _____ (hh:mm)
Result code: _____

Visit 3: Date and Time of arrival

Date: _____ (dd/mm/yyyy)
Time of arrival: ____: _____ (hh:mm)
Time of departure: ____: _____ (hh:mm)
Result code: _____

RESULT CODES:

(1) COMPLETED, 100% of individuals within 200m & at least 30 individuals enrolled (stayed within 200m) (TPE localities only)
(2) COMPLETED, 100% of individuals within 200m & at least 30 individuals enrolled (went beyond 200m) (TPE localities only)
(3) COMPLETED, <100% of individuals within 200m but at least 30 individuals enrolled & 3 visits completed (stayed within 200m) (TPE localities only)
(4) COMPLETED, <100% of individuals within 200m but at least 30 individuals enrolled & 3 visits completed (went beyond 200m) (TPE localities only)
(5) COMPLETED, 100% of individuals within 500m & at least 30 individuals enrolled (RACD localities only)
(6) COMPLETED, <100% of individuals within 500m but at least 30 individuals enrolled & 3 visits completed (RACD localities only)
(7) INCOMPLETE with plans to return
(8) INCOMPLETE with no plans to return
(88) OTHER (SPECIFY) _____

Appendix H. Household level RACD questionnaire

Complete for all households (including households of the index case and households where no one is home or there is no consenting adult available). If this household has previously participated in RACD, a new Household level RACD questionnaire should still be completed.

Screen Type: ☐ Mass Screen ☐ Fever Screen

Neighborhood ID:_____
Automatically generated by the tablet based on index case GPS coordinates. If GPS coordinates within the same 500 m radius as previously implemented index case investigation then assign same Neighborhood ID. Make sure automated number is unique for all tablets.

Index case ID (aciid): _____
Surveillance Agent assigns barcode number to index case

Visit 1: Date: _____ (YY/MM/DD) Time of arrival: ___: _____ __ (hh:mm AM/PM)
Visit 2: Date: _____ (YY/MM/DD) Time of arrival: ___: _____ __ (hh:mm AM/PM)
Visit 3: Date: _____ (YY/MM/DD) Time of arrival: ___: _____ __ (hh:mm AM/PM)
For Visit 1, Date and Time captured automatically when household level questionnaire is saved. There should be 3 date fields, First Entered, Last Modified and Final Entered. On first visit same date is saved on all 3 fields.
For Visit 2, Last Modified and Final Entered should be modified to reflect that day's date and time, this should be done on the Individual level questionnaire and not the household level questionnaire unless edits were made to the household level questionnaire.
For Visit 3, Final entered should be modified to reflect that day's date and time, this should be done on the Individual level questionnaire and not the household level questionnaire unless edits were made to the household level questionnaire.

RACD Household Information

1. Household ID (automatically generated by tablet) _____
   Automatically generated by tablet and should be unique for all tablets to prevent duplication

2. Household description (*if household not a residential premise e.g. Church, describe here*) _____

3. GPS Coordinates
   Latitude: _____
   Longitude: _____
   Automatically captured by tablet when household level questionnaire is saved, allow functionality to edit GPS coordinates by Agents

4. Surveillance Agent Name, check all that apply
   ☐Calsile ☐Sandile ☐Khaya ☐Mathokoza ☐Mduduzi ☐Mukelwe ☐Nombuso
   ☐Nomcebo ☐Nolwazi ☐Senzo ☐Thulani ☐Fanele ☐ Other_____

5. Is household abandoned? ☐ Yes ☐No
   If Yes, continue to next question.
   If No, close and save questionnaire.

6. Is a consenting adult available? ☐ Yes ☐No
   If Yes, continue to next question.
   If No, please indicate number of household members if known ____ (based on neighbor report, otherwise default is "999") and skip to end of questionnaire and move to next home.
   999 denotes unknown number of households members

7. Has this home been sprayed in the past year? ☐ Yes ☐No ☐ Don't Know
   If yes, ask to see spray card to confirm house has been sprayed.
   ☐ Spray card confirmed
   ☐ No spray card
   ☐ Cannot find spray card
   If yes, we're all the houses sprayed? ☐ Yes ☐No ☐ Don't Know
   If yes, do you sleep under a sprayed structure? ☐ Yes ☐No ☐ Don't Know

8. Has this household previously participated in RACD before (during this TPE study period)?
   ☐ Yes ☐No ☐Don't Know
   If yes, how many times before? ____
   If yes, indicate month(s) and year(s) of all previous RACD interventions during this TPE study period
   1. _____ (dd/mm/yyyy)
   2. _____ (dd/mm/yyyy)
   3. _____ (dd/mm/yyyy)

8. List individuals in the household:

	Household head? (check if yes)	Index case? (check if yes)	Name	Scan Barcode	Gender	Date of birth	Present (yes/no)	Notes (why person not present at home and best time to return to speak with person)	Consent obtained for questionnaire (yes/no/ not yet)	Consent obtained for blood collection today (yes/no)	Agreed to be contacted for accepability study (yes/no/ <18 yo, not applicable)	If subject refused blood collection, indicate if refuser survey adminstered (yes/no)
1.												
2.												
Etc.												

Note: Surveillance Agent to assign a barcode even if individual is not present

RACD Household level Dashboard (automatically generated)

	Barcode	Name	Household head? (check if yes)	Index case? (check if yes)	Gender	Age	Consent obtained for questionnaire (yes/no/not yet)	Consent obtained for blood collection today (yes/no)	Blood testing completed (yes/no)	RACD Questionnaire completed (yes/no)	Refuser Questionnaire completed (yes/no)	Notes	
1.													**Edit**
2.													**Edit**
3.													**Edit**
													Add Individual

Editable table listing all household members rising in a household, when a Surveillance Agent clicks on the 'Edit' button they will be shown the questionnaire below to insert information on additional questions not previously posed. When RACD questionnaire for household member is completed the table should refresh and 'Yes' should appear under column for RACD Questionnaire completed and other fields that have since been completed.

RACD Neighborhood Dashboard (automatically generated and includes missed homes)

Note: Use outlined boxes for the "30" criteria

House-hold number	Home of the index case, check if yes	Name of Household head	# of individuals eligible for participation	# of individuals reached (informed consent performed)	# of individuals providing consent for questionnaire	# of questionnaires completed	# of individuals providing consent for initial blood testing	# of individuals RDT performed	# of individuals DBS collected	# of individuals RDT positive	# of RDT+ individuals microtainer collected	# of individuals RDT+ referred for treatment
		Totals:										

Appendix I. RACD Individual questionnaire

1. Barcode: _____
   This field should auto populate after Surveillance Agent clicks on 'Edit' button from RACD Household Level dashboard as barcode was already assigned.

2. Household ID: _____
   This field should auto populate after Surveillance Agent clicks on 'Edit' button from RACD Household Level dashboard as Household ID was already assigned.

3. Consent obtained: ☐ Yes ☐ No ☐ Not yet
   If no, trigger the Refuser Survey
   Questionnaire will only be administered if household member is found at home. Auto-populate 'Not yet' option for consent obtained based on information collected from household level questionnaire. The 'Not yet' option must be greyed out (disabled) though showing that it was a previous selection option. Surveillance Agents must then either select 'Yes' or 'No', with the 'No' option triggering the refuser survey

4. Relation to index case (check all that apply):
   ☐ Immediate Family ☐ Extended family ☐ Neighbor ☐ Visitor ☐ Co-worker ☐ Unknown

5. Nationality:
   ☐ Swaziland☐ Mozambique ☐ South Africa ☐ Other (specify _____)
   (*Provide drop down list of all nationalities)*

6. Occupation (*Drop down list)*:

☐Student	☐Child or minor but not a student	☐Unemployed
☐Farming/Agriculture	☐Manufacturing/Factory	☐Other Manual Labor
☐Small-market sales or trade	☐Office or Clerical Work	☐Other (specify _____**)**

7. Ask: Have you been diagnosed with malaria in the past 12 months? ☐ Yes ☐ No

If yes, ask when,
☐ 6 months to a year ago ☐< 6 months ago ☐ Within the last month ☐ Within the last 2 weeks
☐ Don't know

If yes ask, have you had fever in the last 2 weeks? ☐ Yes ☐No ☐ Don't know

If yes ask, have you been diagnosed with malaria in the last 2 weeks? ☐ Yes ☐No ☐ Don't know

If diagnosed in the last 2 weeks:

Was the diagnosis confirmed by a test? ☐ Yes ☐No ☐ Don't know

What treatment was prescribed? *Check all that apply*
☐ Artemether-lumefantrine
☐ Single dose primaquine
☐ Oral Quinine
☐ IV Quinine
☐ IM Quinine
☐ IV Artesunate
☐ IM Artesunate
☐ Chloroquine
☐ SP/Fansidar
☐ Other (specify _____
☐ Unknown

Was full treatment course completed? ☐ Yes ☐ No ☐ Don't know

Prior Residence and/or Travel History

8. Have you ever lived or stayed in Mozambique for at least 30 consecutive days?
   If yes, approximately how long ago was this visit or stay? _____ yrs _____ mos

9. Have you spent at least one night anywhere else besides your current residence in the past 8 weeks?
   ☐ Yes ☐ No ☐ Don't know
   - ***If no, skip to question 10.***
   - *If yes, ask:* Where did you sleep overnight, when did you sleep there, why did you sleep there, and personal protection? If slept outside Swaziland, also ask about means of travel and border post of re-entry.

Within Swaziland				
Town / Locality / Inkhundla	**Duration of Stay**		**Reason for sleeping away from current residence:** -previous residence -business -holiday -visiting friends/family -other (specify, _____)	**Personal protection** -chemoprophylaxis (specify___) -bednet -mosquito repellent or coil -None
	First Night YY/MM/DD	**Last Night YY/MM/DD**		
a.				
b.				
c.				
d.				
e.				

Outside of Swaziland							
Country	**Province / Town**	**Duration of Stay**		**Reason for sleeping away from current residence:** -previous residence -business -holiday -visiting friends / family -other (specify_____)	**Personal protection** -chemoprophylaxis (specify___) -bednet -mosquito repellent or coil -None	**Means of travel** -Large bus -Kombi (van) -Personal car -Ride share (catch a ride / got a lift) -Airplane -Bicycle -Walked -Other (specify_____)	**Border Post of Re-Entry** - Lavumisa/Golela - Salitje/Onverwacht - Mahamba - Gege/Bothashoop - Sicunusa/Houtkop - Sandlane/Nerston - Ngwenya/Oshoek - Bulembu/Josefsdal - Matsamo/Jeppe's Reef - Mananga - Lomahasha/Namaacha - Mhlumeni/Goba - KMIII International Airport - Other
		First Night YY/MM/DD	**Last Night YY/MM/DD**				
a.							
b.							
c.							
d.							
e.							

10. *Comments or* any other information that is relevant?

_____

11. RDT result:☐positive ☐ negative ☐ not done

If positive, patient referred to local health facility ☐ Yes ☐ No

If no, why? _____

DBS collected ☐Yes ☐ No ☐ Not Done

If DBS not done, why?☐ Patient refused ☐ Other_____

Thank you for our participation in this study.

Appendix J. Household level TPE questionnaire

Complete for all households (including households of the index case and households where no one is home or there is no consenting adult available). Note, in the event that this household has already previously participated in TPE, a new Household level TPE questionnaire should still be completed.

Neighborhood ID:____
Automatically generated by the tablet based on index case GPS coordinates. If GPS coordinates within the same 200 m radius as previously implemented index case investigation then assign same Neighborhood ID. Make sure automated number is unique for all tablets.

Index case ID (aciid): _____
Surveillance Agent assigns barcode number to index case

Visit 1: Date: _____ (YY/MM/DD) Time of arrival: ___: _____ __ (hh:mm AM/PM)
Visit 2: Date: _____ (YY/MM/DD) Time of arrival: ___: _____ __ (hh:mm AM/PM)
Visit 3: Date: _____ (YY/MM/DD) Time of arrival: ___: _____ __ (hh:mm AM/PM)

For Visit 1, Date and Time captured automatically when household level questionnaire is saved. There should be 3 date fields, First Entered, Last Modified and Final Entered. On first visit same date is saved on all 3 fields.
For Visit 2, Last Modified and Final Entered should be modified to reflect that day's date and time, this should be done on the Individual level questionnaire and not the household level questionnaire unless edits were made to the household level questionnaire.
For Visit 3, Final entered should be modified to reflect that day's date and time, this should be done on the Individual level questionnaire and not the household level questionnaire unless edits were made to the household level questionnaire.

TPE Household Information

9. Household ID (automatically generated by tablet) _____
   Automatically generated by tablet and should be unique for all tablets to prevent duplication

10. Household description (*if household not a residential premise e.g. Church, describe here*) _____

11. GPS Coordinates
    Latitude: _____
    Longitude: _____
    Automatically captured by tablet when household level questionnaire is saved, allow functionality to edit GPS coordinates by Agents

12. Surveillance Agent Name, check all that apply
    ☐Calsile ☐Sandile ☐Khaya ☐Mathokoza ☐Mduduzi ☐Mukelwe ☐Nombuso
    ☐Nomcebo ☐Nolwazi ☐Senzo ☐Thulani ☐Fanele ☐ Other_____

13. Is household abandoned? ☐ Yes ☐No
    If Yes, continue to next question.
    If No, close and save questionnaire.

14. Is a consenting adult available? ☐ Yes ☐No
    If Yes, continue to next question.
    If No, please indicate number of household members if known ____ (based on neighbor report, otherwise default is "999") and skip to end of questionnaire and move to next home.
    999 denotes unknown number of households members

15. Has this home been sprayed in the past year? ☐ Yes ☐No ☐ Don't Know

    If yes, ask to see spray card to confirm house has been sprayed.
    ☐ Spray card confirmed
    ☐ No spray card
    ☐ Cannot find spray card

    If yes, we're all the houses sprayed? ☐ Yes ☐No ☐ Don't Know

    If yes, do you sleep under a sprayed structure? ☐ Yes ☐No ☐ Don't Know

16. Has this household previously participated in TPE before (during this TPE study period)?
    ☐ Yes ☐No ☐Don't Know

    If yes, how many times before? ____

    If yes, indicate month(s) and year(s) of all previous TPE interventions during this TPE study period

    1. _____ (dd/mm/yyyy)
    2. _____ (dd/mm/yyyy)
    3. _____ (dd/mm/yyyy

8. List individuals in the household:

	Household head? (check if yes)	Index case? (check if yes)	Name	Scan Barcode	Gender	Date of birth	Present (yes/no)	Notes (why person not present at home and best time to return to speak with person)	Consent obtained for questionnaire (yes/no/not yet)
1.									
2.									
Etc.									

Note: Surveillance Agent to assign a barcode even if individual is not present

TPE Household level Dashboard (automatically generated)

	Barcode	Name	Household head? (check if yes)	Index case? (check if yes)	Gender	Age	Consent obtained for questionnaire (yes/no/not yet)	Questionnaire completed (yes/no)	Eligible for medication	Medication consent	# doses completed	Notes	
1.													**Edit**
2.													**Edit**
3.													**Edit**
													Add Individual

Editable table listing all household members rising in a household, when a Surveillance Agent clicks on the 'Edit' button they will be shown the questionnaire below to insert information on additional questions not previously posed. When TPE questionnaire for household member is completed the table should refresh and 'Yes' should appear under column for TPE Questionnaire completed and other fields that have since been completed.

TPE Neighborhood Dashboard (automatically generated and includes missed homes)

Note: Use outlined boxes for the "30" criteria

Household number	Home of the index case, check if yes	Name of Household head	# of individuals eligible for participation	# of individuals reached (informed consent performed)	# of individuals providing consent for questionnaire	# of questionnaires completed	# of individuals eligible and consented to receive medication	# of individuals received dose 1	# of individuals received dose 2	# of individuals received dose 3
		Totals:								

Appendix K. TPE Individual questionnaire

1. Barcode: _____
   This field should auto populate after Surveillance Agent clicks on 'Edit' button from TPE Household Level dashboard as barcode was already assigned.

2. Household ID: _____
   This field should auto populate after Surveillance Agent clicks on 'Edit' button from TPE Household Level dashboard as Household ID was already assigned.

3. Consent obtained: ☐ Yes ☐ No ☐ Not yet
   If no, trigger the Refuser Survey
   Questionnaire will only be administered if household member is found at home. Auto-populate 'Not yet' option for consent obtained based on information collected from household level questionnaire. The 'Not yet' option must be greyed out (disabled) though showing that it was a previous selection option. Surveillance Agents must then either select 'Yes' or 'No', with the 'No' option triggering the refuser survey

4. Relation to index case (check all that apply):
   ☐ Immediate Family ☐ Extended family ☐ Neighbor ☐ Visitor ☐ Co-worker ☐ Unknown

5. Nationality:
   ☐ Swaziland☐ Mozambique ☐ South Africa ☐ Other (specify _____)
   (*Provide drop down list of all nationalities)*

6. Occupation (*Drop down list)*:
   ☐Student ☐Child or minor but not a student ☐Unemployed
   ☐Farming/Agriculture ☐Manufacturing/Factory ☐Other Manual Labor
   ☐Small-market sales or trade ☐Office or Clerical Work ☐Other (specify _____**)**

7. Ask: Have you been diagnosed with malaria in the past 12 months? ☐ Yes ☐ No

If yes, ask when,
☐ 6 months to a year ago ☐< 6 months ago ☐ Within the last month ☐ Within the last 2 weeks
☐ Don't know

If yes ask, have you had fever in the last 2 weeks? ☐ Yes ☐No ☐ Don't know

If yes ask, have you been diagnosed with malaria in the last 2 weeks? ☐ Yes ☐No ☐ Don't know

If diagnosed in the last 2 weeks:

Was the diagnosis confirmed by a test? ☐ Yes ☐No ☐ Don't know

What treatment was prescribed? *Check all that apply*
☐ Artemether-lumefantrine
☐ Single dose primaquine
☐ Oral Quinine
☐ IV Quinine
☐ IM Quinine
☐ IV Artesunate
☐ IM Artesunate
☐ Chloroquine
☐ SP/Fansidar
☐ Other (specify _____
☐ Unknown

Was full treatment course completed? ☐ Yes ☐ No ☐ Don't know

Prior Residence and/or Travel History

12. Have you ever lived or stayed in Mozambique for at least 30 consecutive days?
    If yes, approximately how long ago was this visit or stay? _____ yrs _____ mos

13. Have you spent at least one night anywhere else besides your current residence in the past 8 weeks?
    ☐ Yes ☐ No ☐ Don't know
    - ***If no, skip to question 10.***
    - *If yes, ask:* Where did you sleep overnight, when did you sleep there, why did you sleep there, and personal protection? If slept outside Swaziland, also ask about means of travel and border post of re-entry.

Within Swaziland				
Town / Locality / Inkhundla	**Duration of Stay**		**Reason for sleeping away from current residence:** -previous residence -business -holiday -visiting friends/family -other (specify, _____)	**Personal protection** -chemoprophylaxis (specify___) -bednet -mosquito repellent or coil -None
	First Night YY/MM/DD	**Last Night YY/MM/DD**		
a.				
b.				
c.				
d.				
e.				

Outside of Swaziland							
Country	**Province / Town**	**Duration of Stay**		**Reason for sleeping away from current residence:** -previous residence -business -holiday -visiting friends/family - Other (specify_____)	**Personal protection** -chemoprophylaxis (specify___) -bednet -mosquito repellent or coil -None	**Means of travel** -Large bus -Kombi (van) -Personal car -Ride share (catch a ride/got a lift) -Airplane -Bicycle -Walked -Other (specify_____)	**Border Post of Re-Entry** - Lavumisa/Golela - Salitje/Onverwacht - Mahamba - Gege/Bothashoop - Sicunusa/Houtkop - Sandlane/Nerston - Ngwenya/Oshoek - Bulembu/Josefsdal - Matsamo/Jeppe's Reef - Mananga - Lomahasha/Namaacha - Mhlumeni/Goba - KMIII International Airport - Other
		First Night YY/MM/DD	**Last Night YY/MM/DD**				
a.							
b.							
c.							
d.							
e.							

Medical History

10. *Weight:* __ __. __ kg
    Tablet should make this question compulsory for all ages

    Ask the following questions to assess for potential criteria excluding participant from receiving antimalarial medication:

11. Are you pregnant or breastfeeding? ☐ Yes ☐ No ☐ Don't know
12. Have you menstruated in the past but not within the past 4 weeks? ☐ Yes ☐ No ☐ Don't know
13. Are you less than 9 months of age? ☐ Yes ☐ No ☐ Don't know
    Tablet should automatically complete this question based on date of birth, select an option and not allow Agent to make changes

14. Are you allergic to have had a past adverse reaction to DP? ☐ Yes ☐ No ☐ Don't know
15. Have you already taken 2 courses of DP in the past year? ☐ Yes ☐ No ☐ Don't know
16. Have you taken DP within the last 2 months? ☐ Yes ☐ No ☐ Don't know
17. Do you have heart, kidney, or liver problems? ☐ Yes ☐ No ☐ Don't know
18. Does your family have a history of heart problems or sudden death? ☐ Yes ☐ No ☐ Don't know
19. In the past month have you taken antimalarial drugs for either treatment or prevention of malaria (mefloquine, halofantrine, lumefantrine, chloroquine, or quinine)? ☐ Yes ☐ No ☐ Don't know
20. Have you had a fever in the past 48 hours, or are otherwise feeling ill? ☐ Yes ☐ No ☐ Don't know
    If Yes, was subject taken to local health facility? ☐ Yes ☐ No
21. Are you currently taking any medications? ☐ Yes ☐ No ☐ Don't know

    If Yes, are you taking any of the following medications? (check all that apply)

    a. ☐ Medicines that effect heart rhythms (such as amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, or sotalol)

    b. ☐ Medicines that treat depression

    c. ☐ Medicines that treat mental health problems (such as phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine)

    d. ☐ Medicines that treat infection (macrolides [such as erythromycin or clarithromycin], fluoroquinolones [such as moxifloxacin or sparfloxacin], medicines for fungal infections [such as imidazole and fluconazole], as well as pentamadine [used to treat a specific type of pnuemonia] and saquinavir [for treatment of HIV])

    e. ☐ Antihistamines used to treat allergies or inflammation (such as terfenadine, astemizole, mizolastine)

    f. ☐ Medicines that treat stomach problems such as cisapride, droperidol, domperidone, or diphemanil

    g. ☐ Medicines to treat cancers (vinca alkaloids, arsenic trioxide), chest pain (bepridil), drug addiction (levomethadyl, methadone), and high cholesterol levels (probucol)

Drug Administration: *(Subject is eligible to receive medication if they weigh at least 7kg and answered "No" to questions 10-19 and are not taking any of the medications listed in 20a-20g)*

22. Is the subject eligible to receive medication? ☐ Yes ☐ No
    Tablet to automatically say Yes or No for eligibility of individual to receive medication based on responses above and criteria provided, options should be greyed out (disabled).
    a. *If yes, indicate regimen administered:*

Check one	Weight band	Color of box	Regimen administered	Subscription
☐	7-12 kg	Bottle	320 mg piperaquine /40 mg dihydroartemisinin tablets, 3 half tablets	½ tablet daily x 3 days
☐	7-12 kg	Pink box	160 mg piperaquine /20 mg dihydroartemisinin tablets, 3 tablets	1 tablet daily x 3 days
☐	13-23 kg	Green box	320 mg piperaquine /40 mg dihydroartemisinin tablets, 3 tablets	1 tablet daily x 3 days
☐	24-35 kg	Orange box	320 mg piperaquine /40 mg dihydroartemisinin tablets, 6 tablets	2 tablet daily x 3 days
☐	36-74 kg	Purple box	320 mg piperaquine /40 mg dihydroartemisinin tablets, 9 tablets	3 tablet daily x 3 days

☐	> 74 kg	Blue bag	320 mg piperaquine /40 mg dihydroartemisinin tablets, 12 tablets	4 tablet daily x 3 days

NOTE: Give lower weight band if weight falls between weight bands.
NOTE: Use of the 320/40 mg or 160/20 mg tablet for children 7-12 kg will depend on drug availability.

b. Was dose #1 directly observed? ☐ Yes ☐ No, indicate reason _____

23. *Comments or* any other information that is relevant?
_____

24. Modified DOT record

Encounter #	Date YY/MM/DD	Time ##:## AM/PM	Oversight (check one)	Comments
1			[ ] Dose #2 DOT by study staff [ ] Dose #2 Self-reported self-administration [ ] Dose #2 Self-administered (reported by someone other than the subject) [ ] Dose #2 Reminded patient to take drug [ ] Dose #2 Indirectly reminded patient to take drug (via close contact) [ ] Dose #2 Other, specify _____	
2			[ ] Dose #2 DOT by study staff [ ] Dose #2 Self-reported self-administration [ ] Dose #2 Self-administered (reported by someone other than the subject) [ ] Dose #2 Reminded patient to take drug [ ] Dose #2 Indirectly reminded patient to take drug (via close contact) [ ] Dose #2 Other, specify _____ --- [ ] Dose #3 DOT by study staff [ ] Dose #3 Self-reported self-administration [ ] Dose #3 Self-administered (reported by someone other than the subject) [ ] Dose #3 Reminded patient to take drug [ ] Dose #3 Indirectly reminded patient to take drug (via close contact) [ ] Dose #3 Other, specify _____	
3			[ ] Dose #2 DOT by study staff [ ] Dose #2 Self-reported self-administration [ ] Dose #2 Self-administered (reported by someone other than the subject) [ ] Dose #2 Reminded patient to take drug [ ] Dose #2 Indirectly reminded patient to take drug (via close contact) [ ] Dose #2 Other, specify _____ --- [ ] Dose #3 DOT by study staff [ ] Dose #3 Self-reported self-administration [ ] Dose #3 Self-administered (reported by someone other than the subject) [ ] Dose #3 Reminded patient to take drug [ ] Dose #3 Indirectly reminded patient to take drug (via close contact) [ ] Dose #3 Other, specify _____	
Rx #3etc.			[ ] Dose #2 DOT by study staff [ ] Dose #2 Self-reported self-administration [ ] Dose #2 Self-administered (reported by someone other than the subject) [ ] Dose #2 Reminded patient to take drug [ ] Dose #2 Indirectly reminded patient to take drug (via close contact) [ ] Dose #2 Other, specify _____ --- [ ] Dose #3 DOT by study staff [ ] Dose #3 Self-reported self-administration [ ] Dose #3 Self-administered (reported by someone other than the subject) [ ] Dose #3 Reminded patient to take drug [ ] Dose #3 Indirectly reminded patient to take drug (via close contact) [ ] Dose #3 Other, specify _____Check one: [ ] DOT by study staff [ ] Self-reported self-administration [ ] Self-administered (reported by someone other than the subject) [ ] Reminded patient to take drug [ ] Indirectly reminded patient to take drug (via close contact) [ ] Other, specify _____	

For return visits for DOT, allow editing of above table for all individuals.

25. Pill count

Date of pill count	*Regimen administered*	*Is your medication packaging still available?*	*IF blister pack available, count number of pills remaining*	*IF blister pack not available, Ask: Approximately how may pills did you take?*	*Other comments*
DD/MM/YY	automatically generated per 22a	[] yes [] no	half tabs [] 1 []2 []3 full tabs (120/20 or 320/40) [ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] 8 [ ] 9	half tabs [] 1 []2 []3 full tabs (120/20 or 320/40) [ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] 8 [ ] 9	

For return visits for pill count, allow editing of above table for all individuals.

26. Ask: Have you experienced any potential side effects from the medication? ☐ *Yes* ☐ *No*

26a If YES, specify:

☐ *cough*
☐ *fever*
☐ *headache*
☐ *lack of energy*
☐ *abdominal pain*
☐ *pale complexion or pallor*
☐ *yellow discoloration of skin or eyes (jaundice)*
☐ *weakness*
☐ *joint pain*
☐ *dark urine*
☐ *nausea*
☐ *vomiting*
☐ *diarrhea*
☐ *chest pain*
☐ *heart palpitations*
☐ *other (specify_____)*

If YES, complete Appendix S. ***Adverse drug reaction (ADR) Report Form***

27. Please explain all measures taken to alleviate these adverse reactions related to the drug

28. Other comments _____

Thank you for our participation in this study.

Appendix L. (1) 6-9 month Follow-Up: Adult Informed Consent Form

Introduction
Greetings! My name is _____. I am conducting surveillance and a research project with the National Malaria Control Program within the Ministry of Health. [You / A member of your community] had malaria about 6-9 months ago. We would like to invite you to participate in a study that will help us understand how to eliminate malaria in your community. Your participation is important, although entirely voluntary. Funding for this study is provided by the Bill & Melinda Gates Foundation.

Why is this study being done?
The purpose of this study is to help Swaziland eliminate malaria. We are evaluating different ways of trying to eliminate malaria. In one group of communities (the first group), everyone was tested for malaria and only people who have malaria were referred for treatment. In another group of communities (the second group), everyone received treatment and prevention for malaria, whether or not they had malaria. Communities received either one of these two interventions. Your community was involved in one of these programs.

Why am I being asked to be a part of this study?
As [you / a member of your community] had malaria 6-9 months ago, we would like to collect a sample of your blood today in order to better understand the body's response to malaria infection. Additionally, near the end of the study, we would like to test everyone in your community for malaria to understand the impact the intervention had on your community. We would like to include you in these follow-up tests.

How many people will take part in this study?
About 600 people will be invited to participate in the study to understand the body's response malaria infection.

What will happen if I take part in this research study?
Right now, you are only being asked to provide consent for the study activities occurring today. Before you participate in any future visit study activities, we will ask you to provide consent again that day.

Today:
Our study team will ask you a few basic questions about you and your experiences with malaria and record your answers on a tablet. We will perform 2 finger pricks to collect a small amount of blood (1/10th of a teaspoon).

Near the end of the study:
In order to assess the impact of our study intervention, our study team will return again near the end of the study (mid 2017) to collect an additional small amount of blood (1/20th of a teaspoon) by finger prick from you. Our study team will also ask you a few basic questions about you and your experiences with malaria and will record your answers on a tablet.

We will perform a rapid test for malaria each time we take a blood sample from you and, if the rapid test shows that you have malaria, we will refer you to the nearest health facility for treatment. We would also like to save a portion of each blood draw for future research studies related to malaria only.

How long will I be in the study?
Today's questionnaire and blood collection will be performed in your home and will take about 10 minutes. The future visit for blood collection will occur in your home and take 5 minutes each time.

Can I stop being in the study?
You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. If at any time, you would like to withdraw your information and/or blood samples from malaria testing, you can contact us. If you choose not to participate in the study or leave the study, there will be no penalty. You will not lose any regular benefits and it will not affect your medical care.

What risks can I expect from being in the study?
There are minimal risks from participating in the interview. The questionnaire does not ask sensitive questions and measures are in place to keep the information you provide confidential. You may feel a brief moment of pain when the blood is being collected and there is a small risk of infection at the site of the finger prick, but the risk is minimal because the process will be done by a well trained officer. Participation or refusal to participate in this study will not affect your care in any way.

Medical care
We do not expect any problems with participating in the study. However, in case you feel unwell at any point during the study as a potential side effect from your participation, you should contact our Study Coordinator and go to your local health facility.

Are there benefits to taking part in the study?
If you are found to have malaria by rapid testing today or at the future visit, you will benefit from being refered for malaria treatment.

What other choices do I have if I do not take part in the study?
You are free to choose not to participate in the study. If you decide not to take part in the study, there will be no penalty to you. You will still get care from the health facility the way you usually do. Even if you do not take part in the study today, you are still eligible to participate in the follow-up blood test near the end of the study.

How will information about me be kept confidential?
We will not inform anyone of your participation in the study and your name will be kept confidential by replacing it with a number/identifier that will be used throughout the study. There may be situations where we need your name, for example for follow up visits. Therefore, we will keep a key linking your name to your study number/identifier. But only key study staff will have access to this information. All information from the study will be kept in locked cabinets or computers.

Organizations that will examine the data are the National Malaria Control Program in Manzini, Swaziland, the Clinton Health Access Initiative in Mbabane, Swaziland and the University of California San Francisco, United States of America. Your name will not appear in any reports or publications.

What are the costs of taking part in this study?
You will not be charged for any of the study procedures.

Will I be paid for taking part in this study?
You will not be paid for taking part in this study.

What are my rights if I take part in this study?
You may choose either to take part or not to take part in the study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you in any way. You will not lose any of your regular benefits, and you can still get your care from your health facility the way you usually do.

Who can I contact in case of injury or if I have future questions about the study?
If you have any questions about this study or your participation, you contact our Study Coordinator at +268 #### ####. If you were found to have malaria today and experience any adverse health events that may be related to treatment, contact your attending Study Nurse at +268 #### ####. If you wish to voice any problems or concerns you may have about how this study is being conducted, please call the office of the Swaziland Ministry of Health's Ethics Committee at +268 2404 7253.

CONSENT
You have been given a copy of this consent form to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled. If you wish to participate in this study, you should indicate how you would like to participate and sign below.

I agree to be interviewed today. ☐ Yes ☐ No

I agree to provide a blood sample for malaria testing today (by a rapid diagnostic test). ☐ Yes ☐ No

I agree to allow a part of today's blood sample to be saved for research purposes related to malaria only. ☐ Yes ☐ No

Date	Name	Signature or finger print

Date	Name of Person Obtaining Consent	Signature of Person Obtaining Consent

WITNESS (only necessary if consent conducted in language other than English or SiSwati)
I witness that this consent form has been read to the participant in the language recorded below, and the participant has agreed to enroll in the study. Language that consent was conducted in:_____.

Date	Name	Signature or finger print of witness

Appendix L. (2) 6-9 month Follow-Up: Parent/Guardian Permission Form for Children

(one form per Parent/Guardian: obtains consent from the Parent/Guardian and permission for multiple children)

Introduction

Greetings! My name is _____. I am conducting surveillance and a research project with the National Malaria Control Program within the Ministry of Health. [You and/or your child(ren) / a member of your community] had malaria about 6-9 months ago. We would like to you to participate in a study that will help us understand how to eliminate malaria in your community. Your participation is important, although entirely voluntary. This study is implemented by the National Malaria Control Program. Funding for this study is provided by the Bill & Melinda Gates Foundation.

Why is this study being done?

The purpose of this study is to help Swaziland eliminate malaria. We are evaluating different ways of trying to eliminate malaria. In one group of communities (the first group), everyone was tested for malaria and only people who have malaria were referred for treatment. In another group of communities (the second group), everyone received treatment and prevention for malaria, whether or not they had malaria. Communities received either one of these two interventions. Your community was involved in one of these programs.

Why are we being asked to be a part of this study?

As [you and or your child(ren) / a member of your community] had malaria 6-9 months ago, we would like to collect a sample of your blood today in order to better understand the body's response to malaria infection. Additionally, near the end of the study, we would like to test everyone in your community for malaria to understand the impact the intervention had on your community. We would like to include you in these follow-up tests.

How many people will take part in this study?

About 600 people will be invited to participate in the study to understand the body's response malaria infection.

What will happen if we take part in this research study?

Right now, you are only being asked to provide consent for the study activities occurring today. Before you or your child(ren) participate in any future visit study activities, we will ask you to provide consent again that day.

Today:

Our study team will ask you a few basic questions about you and your family's experiences with malaria and record your answers on a tablet. We will perform 2 finger pricks to collect a small amount of blood (1/10th of a teaspoon) from you and your child(ren).

Near the end of the study:

In order to assess the impact of our study intervention, our study team will return again near the end of the study (mid 2017) to collect an additional small amount of blood (1/20th of a teaspoon) by finger prick from your family. Our study team will also ask you a few basic questions about your family's experiences with malaria and will record your answers on a tablet.

We will perform a rapid test for malaria each time we take a blood sample and, if the rapid test shows that any of you have malaria, we will refer all infected individual(s) to the nearest health facility for treatment. We would also like to save a portion of each blood draw for future research studies related to malaria only.

How long will we be in the study?

Today's questionnaire and blood collection will be performed in your home. The questionnaire will take about 5 minutes and blood collection will take about 5 minutes per person. The future visit for blood collection will occur in your home and take 5 minutes per person.

What are our rights if we take part in this study? Can we stop being in the study?

You may choose either to take part or not to take part in the study. If you decide to take part in this study, you or your child(ren) may leave the study at any time. If at any time, you would like to withdraw your and/or your child(ren)'s information and/or withdraw blood samples from malaria testing, you can contact us. If you choose not to participate in the study or leave the study, there will be no penalty to you or your family. You will not lose any regular benefits and it will not affect your medical care.

What risks can we expect from being in the study?

There are minimal risks from participating in the interview. The questionnaire does not ask sensitive questions and measures are in place to keep the information you provide confidential. There may be a brief moment of pain when the blood is being collected and there is a small risk of infection at the site of the finger prick, but the risk is minimal because the process will be done by a well trained officer. Participation or refusal to participate in this study will not affect your care in any way.

Medical care.

We do not expect any problems with participating in the study. However, in case you or your child(ren) feel unwell at any point during the study as a potential side effect from your participation, you should contact our Study Coordinator and go to your local health facility.

Are there benefits to taking part in the study?

If you or your child(ren) are found to have malaria by rapid testing today or at the future visit, they will benefit from being refered for malaria treatment.

What other choices do we have if we do not take part in the study?

If you decide not to take part in the study, there will be no penalty. You and your child(ren) will still get care from the health facility the way you usually do. Even if you do not take part in the study today, you and your child(ren) are still eligible to participate in the follow-up blood test near the end of the study.

How will information about us be kept confidential?

We will not inform anyone of you or your child(ren)'s participation in the study and your names will be kept confidential by replacing them with numbers/identifiers that will be used throughout the study. There may be situations where we need your or your child(ren)'s name(s), for example for follow up visits. Therefore, we will keep a key linking your names to your study numbers/identifiers. But only key study staff will have access to this information. All information from the study will be kept in locked cabinets or computers. Organizations that will examine the data are the National Malaria Control Program in Manzini, Swaziland, the Clinton Health Access Initiative in Mbabane, Swaziland and the University of California San Francisco, United States of America. Your and your child(ren)'s name will not appear in any reports or publications.

What are the costs of taking part in this study?
You will not be charged for any of the study procedures.

Will we be paid for taking part in this study?
You will not be paid for taking part in this study.

What are our rights if we take part in this study?
If you decide to take part in the study, you and/or your child(ren) may leave the study at any time. No matter what decision you make, there will be no penalty in any way. Your family will not lose any regular benefits, and your family can still get care from the health facility the way they usually do.

Who can I contact in case of injury or if I have future questions about the study?
If you have any questions about this study or your or your child(ren)'s participation, you can contact our Study Coordinator at +268 #### ####. If you or your child(ren) were found to have malaria today and experienced any adverse health events that may be related to treatment, contact your attending Study Nurse at +268 #### ####. If you wish to voice any problems or concerns you may have about how this study is being conducted, please call the office of the Swaziland Ministry of Health's Ethics Committee at +268 2404 7253.

CONSENT
You have been given a copy of this consent form to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. Your child(ren) are unable to consent for themselves because they are less than 18 years old. By signing this form, you are giving permission for your child(ren) or ward(s) to participate in the study. You have the right to decline to participate or to have your child(ren) or ward(s) participate or to withdraw them at any point in this study without penalty or loss of benefits to which you or your family are otherwise entitled. If you wish to participate and have your child(ren) participate in this study, you should indicate how you would like to participate and sign below.

Number of children (<18 years old) that I consent may participate in the study: _____.

I agree to be interviewed today. ☐ Yes ☐ No

I agree have my child(ren) be interviewed today, if requested by study staff. ☐ Yes ☐ No

I agree to provide a blood sample for malaria testing today (by a rapid diagnostic test), if requested by study staff. ☐ Yes ☐ No

I agree to have my child(ren) provide a blood sample for malaria testing today (by a rapid diagnostic test), if requested by study staff. ☐ Yes ☐ No

I agree to allow a part of my blood sample to be saved for for research purposes related to malaria only. ☐ Yes ☐ No

I agree to allow a part of my child(ren)'s blood sample(s) to be saved for research purposes related to malaria only. ☐ Yes ☐ No

Date	Name of Parent/Guardian	Signature or fingerprint of Parent/Guardian

Name(s) of children (If indicated, list names of additional children on the back of the form):

Child #1	Child #2	Child #3	Child #4
Child #5	Child #6	Child #7	Child #8

Date	Name of Person Obtaining Consent	Signature of Person Obtaining Consent

WITNESS (only necessary if consent conducted in language other than English or SiSwati)
I witness that this consent form has been read to the participant in the language recorded below, and the participant has agreed to enroll in the study. Language that consent was conducted in:_____.

Date	Name	Signature or finger print of witness

Appendix L. (3) 6-9 month Follow-Up: Minor (12-17yrs) Assent Form

Introduction
Greetings! My name is _____. I am conducting surveillance and a research project with the National Malaria Control Program within the Ministry of Health. [You / A member of your community] had malaria about 6-9 months ago. We would like to invite you to participate in a study that will help us understand how to eliminate malaria in your community. Your participation is important, although entirely voluntary. Funding for this study is provided by the Bill & Melinda Gates Foundation.

Why is this study being done?
The purpose of this study is to help Swaziland eliminate malaria. We are evaluating different ways of trying to eliminate malaria. In one group of communities (the first group), everyone was tested for malaria and only people who have malaria were referred for treatment. In another group of communities (the second group), everyone received treatment and prevention for malaria, whether or not they had malaria. Communities received either one of these two interventions. Your community was involved in one of these programs.

Why am I being asked to be a part of this study?
As [you / a member of your community] had malaria 6-9 months ago, we would like to collect a sample of your blood today in order to better understand the body's response to malaria infection. Additionally, near the end of the study, we would like to test everyone in your community for malaria to understand the impact the intervention had on your community. We would like to include you in these follow-up tests.

How many people will take part in this study?
About 600 people will be invited to participate in the study to understand the body's response malaria infection.

What will happen if I take part in this research study?
Right now, you are only being asked to provide assent for the study activities occurring today. Before you participate in any future visit study activities, we will ask you to provide assent again that day.

Today:
Our study team will ask you a few basic questions about you and your experiences with malaria and record your answers on a tablet. We will perform 2 finger pricks to collect a small amount of blood (1/10th of a teaspoon).

Near the end of the study:
In order to assess the impact of our study intervention, our study team will return again near the end of the study (mid 2017) to collect an additional small amount of blood (1/20th of a teaspoon) by finger prick from you. Our study team will also ask you a few basic questions about you and your experiences with malaria and will record your answers on a tablet.

We will perform a rapid test for malaria each time we take a blood sample from you and, if the rapid test shows that you have malaria, we will refer you to the nearest health facility for treatment. We would also like to save a portion of each blood draw for future research studies related to malaria only.

How long will I be in the study?
Today's questionnaire and blood collection will be performed in your home and will take about 10 minutes. The future visit for blood collection will occur in your home and take 5 minutes each time.

What are my rights if I take part in this study? Can I stop being in the study?
With the permission of your parent or guardian, you may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. If at any time, you would like to withdraw your information and/or withdraw blood samples from malaria testing, you can have your parent or guardian contact us. If your parent or guardian wants you to withdraw from the study, you must withdraw. If you choose not to participate in the study or leave the study, there will be no penalty to you or your family. You will not lose any regular benefits and it will not affect your medical care.

What risks can I expect from being in the study?
There are minimal risks from participating in the interview. The questionnaire does not ask sensitive questions and measures are in place to keep the information you provide confidential. You may feel a brief moment of pain when the blood is being collected and there is a small risk of infection at the site of the finger prick, but the risk is minimal because the process will be done by a well trained officer. Participation or refusal to participate in this study will not affect your care in any way.

Medical care.
We do not expect any problems with participating in the study. However, in case you feel unwell at any point during the study as a potential side effect from your participation, you should have your parent/guardian contact our Study Coordinator and bring you to your local health facility.

Are there benefits to taking part in the study?
If you are found to have malaria by rapid testing today or at the future visit, you will benefit from being refered for malaria treatment.

What other choices do I have if I do not take part in the study?
You are free to choose not to participate in the study. If you decide not to take part in the study, there will be no penalty to you. You will still get care from the health facility the way you usually do. Even if you do not take part in the study today, you are still eligible to participate in the follow-up blood test near the end of the study.

How will information about me be kept confidential?
We will not inform anyone of your participation in the study and your name will be kept confidential by replacing it with a number/identifier that will be used throughout the study. There may be situations where we need your name, for example for follow up visits. Therefore, we will keep a key linking your name to your study number/identifier. But only key study staff will have access to this information. All information from the study will be kept in locked cabinets or computers. Organizations that will examine the data are the National Malaria Control Program in Manzini, Swaziland, the Clinton Health Access Initiative in Mbabane, Swaziland and the University of California San Francisco, United States of America. Your name will not appear in any reports or publications.

What are the costs of taking part in this study?
You will not be charged for any of the study procedures.

Will I be paid for taking part in this study?
You will not be paid for taking part in this study.

What are my rights if I take part in this study?
With your parent or guardian's permission, you may choose either to take part or not to take part in the study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you in any way. You will not lose any of your regular benefits, and you can still get your care from your health facility the way you usually do.

Who can I contact in case of injury or if I have future questions about the study?
If you have any questions about this study or your participation, you can have your parent/guardian contact our Study Coordinator at +268 #### ####. If you were found to have malaria today and experience any adverse health events that may be related to treatment, have your parent/guardian contact your attending Study Nurse at +268 #### ####. If you wish to voice any problems or concerns you may have about how this study is being conducted, please have your parent/guardian call the office of the Swaziland Ministry of Health's Ethics Committee at +268 2404 7253.

ASSENT
You have been given a copy of this assent form to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should indicate how you would like to participate and sign below.

This study was explained to me clearly.	☐ Yes	☐ No
I agree to be interviewed today.	☐ Yes	☐ No
I agree to provide a blood sample for malaria testing today (by a rapid diagnostic test).	☐ Yes	☐ No
I agree to allow a part of today's blood sample to be saved for research purposes related to malaria only.	☐ Yes	☐ No

Date	Name of Minor	Signature or finger print of Minor

Date	Name of Person Obtaining Consent	Signature of Person Obtaining Consent

WITNESS (only necessary if assent conducted in language other than English or SiSwati)
I witness that this assent form has been read to the participant in the language recorded below, and the participant has agreed to enroll in the study. Language that assent was conducted in:_____.

Date	Name	Signature or finger print of witness

Appendix M. 6-9 month follow-up questionnaire

1. Investigation conducted by, (check all that apply)
   ☐Badelisile☐Calsile☐Gcinumuzi☐Khaya☐Mathokoza☐Mduduzi☐Mpendulo☐Nombuso
   ☐Nomcebo☐Nomkhosi☐Senzo☐Thulani☐Vusani☐ Other_____
2. Scan Barcode
3. Subject's Name _____
4. Gender ☐ Male ☐Female
5. Date of birth |__|__|/|__|__|/|__|__|
   date month year
6. Inkhundla _____
7. Locality _____
8. Patient contact information
   a. Telephone number 1: _____
   b. Telephone number 2: _____
9. GPS coordinates of home (can skip and record later, as interview may not be conducted at subject's home)
   S ___° ___' ___"
   E ___° ___' ___"
10. Consent obtained: ☐ Yes ☐ No
11. *Ask,* have you had fever in the last 2 weeks? ☐ Yes ☐No ☐ Don't know
12. *Ask:* Have you been diagnosed with malaria in the past 12 months? ☐ Yes ☐ No

    If yes, ask when,
    - ☐ 6 months to a year ago
    - ☐< 6 months ago
    - ☐ Within the last month
    - ☐ Within the last 2 weeks
    - ☐ Don't know

    If diagnosed in the last 2 weeks:

    Was the diagnosis confirmed by a test?
    - ☐ Yes
    - ☐No
    - ☐ Don't know

    What treatment was prescribed? *Check all that apply*
    - ☐ Artemether-lumefantrine
    - ☐ Single dose primaquine
    - ☐ Oral Quinine
    - ☐ IV Quinine
    - ☐ IM Quinine
    - ☐ IV Artesunate
    - ☐ IM Artesunate
    - ☐ Chloroquine
    - ☐ SP/Fansidar
    - ☐ Other (specify _____
    - ☐ Unknown

    Was full treatment course completed? ☐ Yes ☐ No ☐ Don't know

Prior Residence and/or Travel History

14. Have you ever lived or stayed in Mozambique for at least 30 consecutive days?
    If yes, approximately how long ago was this visit or stay? _____ yrs _____ mos

15. Have you spent at least one night anywhere else besides your current residence in the past 8 weeks?
    ☐ Yes ☐ No ☐ Don't know
    - ***If no, skip to question 10.***
    - *If yes, ask:* Where did you sleep overnight, when did you sleep there, why did you sleep there, and personal protection? If slept outside Swaziland, also ask about means of travel and border post of re-entry.

Within Swaziland				
Town / Locality / Inkhundla	**Duration of Stay**		**Reason for sleeping away from current residence:** -previous residence -business -holiday -visiting friends/family -other (specify, _____)	**Personal protection** -chemoprophylaxis (specify___) -bednet -mosquito repellent or coil -None
	First Night YY/MM/DD	**Last Night YY/MM/DD**		
a.				
b.				
c.				
d.				
e.				

Outside of Swaziland							
Country	**Province / Town**	**Duration of Stay**		**Reason for sleeping away from current residence:** -previous residence -business -holiday -visiting friends / family -other (specify_____)	**Personal protection** -chemoprophylaxis (specify___) -bednet -mosquito repellent or coil -None	**Means of travel** -Large bus -Kombi (van) -Personal car -Ride share (catch a ride / got a lift) -Airplane -Bicycle -Walked -Other (specify_____)	**Border Post of Re-Entry** - Lavumisa/Golela - Salitje/Onverwacht - Mahamba - Gege/Bothashoop - Sicunusa/Houtkop - Sandlane/Nerston - Ngwenya/Oshoek - Bulembu/Josefsdal - Matsamo/Jeppe's Reef - Mananga - Lomahasha/Namaacha - Mhlumeni/Goba - KMIII International Airport - Other
		First Night YY/MM/DD	**Last Night YY/MM/DD**				
a.							
b.							
c.							
d.							
e.							

16. *Comments or* any other information that is relevant?

_____

17. RDT result:☐positive ☐ negative ☐ not done

If positive, patient referred to local health facility ☐ Yes ☐ No

If no, why? _____

DBS collected ☐Yes ☐ No ☐ Not Done

If DBS not done, why?☐ Patient refused ☐ Other_____

Thank you for our participation in this study.

Appendix N. (1) Resident End-line Survey
Adult Informed Consent Form

Introduction
Greetings! My name is _____. I am conducting surveillance and a research project with the National Malaria Control Program within the Ministry of Health. We recently implemented a malaria intervention in your community. In order to evaluate the impact of that intervention, we have now returned for blood testing in your community. Your participation is important, although entirely voluntary. Funding for this study is provided by the Bill & Melinda Gates Foundation.

Why is this study being done?
The purpose of this study is to help Swaziland eliminate malaria. We are evaluating different ways of trying to eliminate malaria. In one group of communities (the first group), everyone was tested for malaria and only people who have malaria were referred for treatment. In another group of communities (the second group), everyone received treatment and prevention for malaria, whether or not they had malaria. Communities received either one of these two interventions. Your community was involved in one of these programs. We are now testing everyone to see how many people have malaria after the program.

How many people will take part in this study?
About 4500 people were in the first group of communities and 4500 people were in the second group of communities. 8100 people will be included in the end-line survey.

What will happen if I take part in this research study?
We would like to collect a small amount of blood from you today, 1/20th of a teaspoon by finger prick. We will perform a rapid test for malaria and will provide a referral to the nearest health facility for treatment if you are found to be infected. We would also like to save a portion of the blood draw for future research studies related to malaria only. Our study team will also ask you a few basic questions about you and your experiences with malaria and will record your answers on a tablet.

How long will I be in the study?
Today's blood collection and interview will be performed in your home and will take about 5 minutes.

Can I stop being in the study?
If you decide to take part in this study, you may leave the study at any time. If at any time, you would like to withdraw your blood samples from malaria testing, you can contact us. If you choose not to participate in the study or leave the study, there will be no penalty to you or your family. You will not lose any regular benefits and it will not affect your medical care.

What risks can I expect from being in the study?
You may feel a brief moment of pain when the blood is being collected and there is a small risk of infection at the site of the finger prick, but the risk is minimal because the process will be done by a well trained officer.

Medical care.
We do not expect any problems with participating in the study. However, in case you feel unwell at any point during the study as a potential side effect from your participation, you should contact our Study Coordinator and go to your local health facility.

Are there benefits to taking part in the study?
If you are found to have malaria by rapid testing today, you will benefit from being refered for malaria treatment.

How will information about me be kept confidential?
We will not inform anyone of your participation in the study and your name will be kept confidential by replacing it with a number/identifier that will be used throughout the study. Only key study staff will have access to this information. All information from the study will be kept in locked cabinets or computers. Organizations that will examine the data are the National Malaria Control Program in Manzini, Swaziland, the Clinton Health Access Initiative in Mbabane, Swaziland and the University of California San Francisco, United States of America. Your name will not appear in any reports or publications.

What are the costs of taking part in this study?
You will not be charged for any of the study procedures.

Will I be paid for taking part in this study?
You will not be paid for taking part in this study.

What are my rights if I take part in this study?
You may choose either to take part or not to take part in the study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you in any way. You will not lose any of your regular benefits, and you can still get your care from your health facility the way you usually do.

Who can I contact in case of injury or if I have future questions about the study?
If you have any questions about this study or your participation, you can contact our Study Coordinator at +268 #### ####. If you were found to have malaria today and experience any adverse health events that may be related to treatment, contact your attending Study Nurse at +268 #### ####. If you wish to voice any problems or concerns you may have about how this study is being conducted, please call the office of the Swaziland Ministry of Health's Ethics Committee at +268 2404 7253.

CONSENT

You have been given a copy of this consent form to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled. If you wish to participate in this study, you should indicate how you would like to participate and sign below.

I agree to be interviewed today. ☐ Yes ☐ No

I agree to provide a blood sample for malaria testing today (by a rapid diagnositc test). ☐ Yes ☐ No

I agree to allow a part of my blood sample to be saved for research purposes related to malaria only. ☐ Yes ☐ No

Date	Name	Signature or finger print

Date	Name of Person Obtaining Consent	Signature of Person Obtaining Consent

WITNESS (only necessary if consent conducted in language other than English or SiSwati)

I witness that this consent form has been read to the participant in the language recorded below, and the participant has agreed to enroll in the study.

Language that consent was conducted in:_____.

Date	Name	Signature or finger print of witness

Appendix N. (2) Resident End-line Survey
Parent / Guardian Permission Form for Children <12 years

(one form per Parent/Guardian: obtains consent from the Parent/Guardian and permission for multiple children)

Introduction

Greetings! My name is _____. I am conducting surveillance and a research project with the National Malaria Control Program within the Ministry of Health. We recently implemented a malaria intervention in your community. In order to evaluate the impact of that intervention, we have now returned for blood testing in your community. Your participation is important, although entirely voluntary. Funding for this study is provided by the Bill & Melinda Gates Foundation.

Why is this study being done?

The purpose of this study is to help Swaziland eliminate malaria. We are evaluating different ways of trying to eliminate malaria. In one group of communities (the first group), everyone was tested for malaria and only people who have malaria were referred for treatment. In another group of communities (the second group), everyone received treatment and prevention for malaria, whether or not they had malaria. Communities received either one of these two interventions. Your community was involved in one of these programs. We are now testing everyone to see how many people have malaria after the program.

How many people will take part in this study?

About 4500 people were in the first group of communities and 4500 people were in the second group of communities. 8100 people will be included in the end-line survey.

What will happen if we take part in this research study?

We would like to collect a small amount of blood from you and your child(ren) today, 1/20th of a teaspoon by finger prick. Each blood collection should take about 5 minutes. We will perform a rapid test for malaria and will provide a referral to the nearest health facility for treatment if you or your child(ren) are found to be infected. We would also like to save a portion of the blood draw for future research studies related to malaria only. Our study team will also ask you a few basic questions about your family's experiences with malaria and will record your answers on a tablet.

How long will we be in the study?

Today's blood collection and interview will be performed in your home and will take about 5 minutes per person.

Can we stop being in the study?

If you decide to take part in this study, you and/or your child(ren) may leave the study at any time. If at any time, you would like to withdraw your and/or your child(ren)'s blood samples from malaria testing, you can contact us. If you choose not to participate in the study or leave the study, there will be no penalty to your child(ren) or your family. You will not lose any regular benefits and it will not affect your family's medical care.

What risks can we expect from being in the study?

There may be a brief moment of pain when the blood is being collected and there is a small risk of infection at the site of the finger prick, but the risk is minimal because the process will be done by a well trained officer.

Medical care.

We do not expect any problems with participating in the study. However, in case you or your child(ren) feel unwell at any point during the study as a potential side effect from their participation, you should contact our Study Coordinator and go to your local health facility.

Are there benefits to taking part in the study?

If you or your child(ren) are found to have malaria on rapid testing today, they will benefit from being refered for malaria treatment.

How will information about us be kept confidential?

We will not inform anyone of your or your child(ren)'s participation in the study and your name(s) will be kept confidential by replacing them with number(s)/identifier(s) that will be used throughout the study. Only key study staff will have access to this information. All information from the study will be kept in locked cabinets or computers. Organizations that will examine the data are the National Malaria Control Program in Manzini, Swaziland, the Clinton Health Access Initiative in Mbabane, Swaziland and the University of California San Francisco, United States of America. Your name(s) will not appear in any reports or publications.

What are the costs of taking part in this study?

You will not be charged for any of the study procedures.

Will we be paid for taking part in this study?

You will not be paid for taking part in this study.

What are our rights if we take part in this study?

You may choose either to take part or not to take part in the study. If you decide to take part in the study, you and/or your child(ren) may leave the study at any time. No matter what decision you make, there will be no penalty to you or your family in any way. You and your child(ren) will not lose any of your regular benefits, and you can still get care from your health facility the way you usually do.

Who can I contact in case of injury or if I have future questions about the study?

If you have any questions about this study or your participation, you can contact our Study Coordinator at +268 #### ####. If you or your child(ren) were found to have malaria today and experience any adverse health events that may be related to treatment, contact your attending Study Nurse at +268 #### ####. If you wish to voice any problems or concerns you may have about how this study is being conducted, please have your parent/guardian call the office of the Swaziland Ministry of Health's Ethics Committee at +268 2404 7253.

CONSENT

You have been given a copy of this consent form to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. Your child(ren) are unable to consent for themselves because they are less than 18 years old. By signing this form, you are giving permission for you and your child(ren) or ward(s) to participate in the study. You have the right to decline participate or to withdraw at any point in this study without penalty or loss of benefits to which you or your family are otherwise entitled. If you wish to participate or have your child(ren) participate in this study, you should indicate how you would like to participate and sign below.

Number of children (<18 years old) that I consent may participate in the study: _____.

I agree to be interviewed today. ☐ Yes ☐ No

I agree to have my child(ren) be interviewed today, if requested by study staff. ☐ Yes ☐ No

I agree to provide a blood sample for malaria testing today (by a rapid diagnositc test). ☐ Yes ☐ No

I agree to have my child(ren) provide a blood sample for malaria testing today (by a rapid diagnositc test). ☐ Yes ☐ No

I agree to allow a part of my blood sample to be saved for research purposes related to malaria only. ☐ Yes ☐ No

I agree to allow a part of my child(ren)'s blood sample(s) to be saved for research purposes related to malaria only. ☐ Yes ☐ No

_____	_____	_____
Date	Name of Parent/Guardian	Signature or fingerprint of Parent/Guardian

Name(s) of children (If indicated, list names of additional children on the back of the form):

_____	_____	_____	_____
Child #1	Child #2	Child #3	Child #4
_____	_____	_____	_____
Child #5	Child #6	Child #7	Child #8

_____	_____	_____
Date	Name of Person Obtaining Consent	Signature of Person Obtaining Consent

WITNESS (only necessary if consent conducted in language other than English or SiSwati)

I witness that this consent form has been read to the participant in the language recorded below, and the participant has agreed to enroll in the study.

Language that consent was conducted in:_____.

_____	_____	_____
Date	Name	Signature or finger print of witness

Appendix N. (3) Resident End-line Survey
Minor (12-17yr) Assent Form

Introduction
Greetings! My name is _____. I am conducting surveillance and a research project with the National Malaria Control Program within the Ministry of Health. We recently implemented a malaria intervention in your community. In order to evaluate the impact of that intervention, we have now returned for blood testing in your community. Your participation is important, although entirely voluntary. Funding for this study is provided by the Bill & Melinda Gates Foundation.

Why is this study being done?
The purpose of this study is to help Swaziland eliminate malaria. We are evaluating different ways of trying to eliminate malaria. In one group of communities (the first group), everyone was tested for malaria and only people who have malaria were referred for treatment. In another group of communities (the second group), everyone received treatment and prevention for malaria, whether or not they had malaria. Communities received either one of these two interventions. Your community was involved in one of these programs. We are now testing everyone to see how many people have malaria after the program.

How many people will take part in this study?
About 4500 people were in the first group of communities and 4500 people were in the second group of communities. 8100 people will be included in the end-line survey.

What will happen if I take part in this research study?
We would like to collect a small amount of blood from you today, 1/20th of a teaspoon by finger prick. We will perform a rapid test for malaria and will provide a referral to the nearest health facility for treatment if you are found to be infected. We would also like to save a portion of the blood draw for future research studies related to malaria only. Our study team will also ask you a few basic questions about you and your experiences with malaria and will record your answers on a tablet.

How long will I be in the study?
Today's blood collection and interview will be performed in your home and will take about 5 minutes.

Can I stop being in the study?
If you decide to take part in this study, you may leave the study at any time. If at any time, you would like to withdraw your information and/or withdraw blood samples from malaria testing, your parent or guardian can contact us. If your parent or guardian wants you to withdraw from the study, you must withdraw. If you choose not to participate in the study or leave the study, there will be no penalty to you or your family. You will not lose any regular benefits and it will not affect your medical care.

What risks can I expect from being in the study?
You may feel a brief moment of pain when the blood is being collected and there is a small risk of infection at the site of the finger prick, but the risk is minimal because the process will be done by a well trained officer.

Medical care.
We do not expect any problems with participating in the study. However, in case you feel unwell at any point during the study as a potential side effect from your participation, you should have your parent/guardian contact our Study Coordinator and bring you to your local health facility.

Are there benefits to taking part in the study?
If you are found to have malaria by rapid testing today, you will benefit from being refered for malaria treatment.

How will information about me be kept confidential?
We will not inform anyone of your participation in the study and your name will be kept confidential by replacing it with a number/identifier that will be used throughout the study. Only key study staff will have access to this information. All information from the study will be kept in locked cabinets or computers. Organizations that will examine the data are the National Malaria Control Program in Manzini, Swaziland, the Clinton Health Access Initiative in Mbabane, Swaziland and the University of California San Francisco, United States of America. Your name will not appear in any reports or publications.

What are the costs of taking part in this study?
You will not be charged for any of the study procedures.

Will I be paid for taking part in this study?
You will not be paid for taking part in this study.

What are my rights if I take part in this study?
With your parent or guardian's permission, you may choose either to take part or not to take part in the study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you in any way. You will not lose any of your regular benefits, and you can still get your care from your health facility the way you usually do.

Who can I contact in case of injury or if I have future questions about the study?
If you have any questions about this study or your participation, you can have your parent/guardian contact our Study Coordinator at +268 #### ####. If you were found to have malaria today and experience any adverse health events that may be related to treatment, have your parent/guardian contact your attending Study Nurse at +268 #### ####. If you wish to voice any problems or concerns you may have about how this study is being conducted, please have your parent/guardian call the office of the Swaziland Ministry of Health's Ethics Committee at +268 2404 7253.

ASSENT

You have been given a copy of this assent form to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled. If you wish to participate in this study, you should indicate how you would like to participate and sign below.

This study was explained to me clearly. ☐ Yes ☐ No

I agree to be interviewed today. ☐ Yes ☐ No

I agree to provide a blood sample for malaria testing today (by a rapid diagnositc test). ☐ Yes ☐ No

I agree to allow a part of today's blood sample to be saved by
study staff for future testing (for research purposes only). ☐ Yes ☐ No

Date	Name of Minor	Signature or fingerprint of Minor

Date	Name of Person Obtaining Consent	Signature of Person Obtaining Consent

WITNESS (only necessary if assent conducted in language other than English or SiSwati)

I witness that this assent form has been read to the participant in the language recorded below, and the participant has agreed to enroll in the study.

Language that assent was conducted in:_____.

Date	Name	Signature or finger print of witness

Appendix O. Household level end-line survey (to be completed mid 2017)

	Barcode (from last visit)	Name	House hold head (check if yes)	Index case (check if yes)	Gender	Date of birth	Consent obtained for today's blood collection (yes/no)	Participated in intervention (yes/no)	Have you been diagnosed with malaria since you first participated in the study intervention? Yes/No If yes list date or dates _____ YY/MM/DD	Have you had fever in the past 2 weeks? (yes/no)	Have you take antimalarial medication in the past 2 months? Yes/No If yes, what treatment was prescribed? *Check all that apply* ☐AL (Coartem) ☐ Single dose primaquine ☐ Oral Quinine ☐ IV Quinine ☐ IM Quinine ☐ IV Artesunate ☐ IM Artesunate ☐Chloroquine ☐ SP/Fansidar ☐ Other (specify_____) ☐Unknown Was full treatment course completed? ☐Yes ☐No ☐Don't know On what day was the last treatment started? _____ YY/MM/DD	Have you spent at least one night outside of this village in the past 8 weeks? If yes, complete travel information below.	DBS collected today? (yes/no)	Notes
1.														**Edit**
2.														**Edit**
Etc.														**Add Individual**

Note: Shaded areas will be automatically generated from the all previous visits to this household. For each individual, confirm this data. If
Note: Add a new line for individuals

Travel information

Within Swaziland			Outside of Swaziland		
Village / town/ District where you have spent the night(s)	Duration of stay		Country/Province/Town where you have spent the night(s)	Duration of stay	
	First Night DD/MM/YY	Last Night DD/MM/YY		First Night DD/MM/YY	Last Night DD/MM/YY

Appendix P. End-line Individual questionnaire

Patient Details

1. Patient Name _____
2. Date of birth |___|___|/|___|___|/|___|___|
   date month year
3. Gender ☐ Male ☐Female
4. Inkhundla _____
5. Locality _____
6. Study ID: _____
7. Household ID: _____
8. Consent obtained: ☐ Yes ☐ No
9. *Ask:* Did you participate in the initial study intervention?
   - ☐ TPE Arm
   - ☐ RACD Arm
   - ☐ Did not participate

   If yes, ask: Have you taken malaria medication as a part of this study? ☐ Yes ☐ No

   If yes, ask: What malaria medication did you take?
   - ☐ Dihydroartemisinin-piperaquine (Eurartesim)
   - ☐Artemether-lumefantrine (Coartem)
   - ☐ Other (specify _____
   - ☐Unknown

   If yes, ask: Did you experience any adverse events that you think may have been related to the malaria medication? ☐ Yes ☐ No

   If yes, ask: Please describe these adverse events.
   _____
   _____
10. *Ask:* Have you been diagnosed with malaria in the past 12 months? ☐ Yes ☐ No

If yes, ask when,
- ☐ 6 months to a year ago
- ☐< 6 months ago
- ☐ Within the last month
- ☐ Within the last 2 weeks
- ☐ Don't know

If yes ask, have you had fever in the last 2 weeks? ☐ Yes ☐No ☐ Don't know
If yes ask, have you been diagnosed with malaria in the last 2 weeks? ☐ Yes ☐No ☐ Don't know
If diagnosed in the last 2 weeks:

Was the diagnosis confirmed by a test? ☐ Yes ☐No ☐ Don't know
What treatment was prescribed? *Check all that apply*
- ☐Artemether-lumefantrine
- ☐ Single dose primaquine
- ☐ Oral Quinine
- ☐ IV Quinine
- ☐ IM Quinine
- ☐Chloroquine
- ☐ SP/Fansidar
- ☐ Other (specify _____
- ☐Unknown

Was full treatment course completed? ☐ Yes ☐ No ☐ Don't know

Prior Residence and/or Travel History

11. Have you ever lived or stayed in Mozambique for at least 30 consecutive days?
    If yes, approximately how long ago was this visit or stay? _____ yrs _____ mos

12. Have you spent at least one night anywhere else besides your current residence in the past 8 weeks?
    ☐ Yes ☐ No ☐ Don't know
    - ***If no, skip rest of questions.***
    - *If yes, ask:* Where did you sleep overnight, when did you sleep there, why did you sleep there, and personal protection? If slept outside Swaziland, also ask about means of travel and border post of re-entry.

Within Swaziland				
Town / Locality / Tinkhundla	**Duration of Stay**		**Reason for sleeping away from current residence:** -previous residence -business -holiday -visiting friends/family -other (specify, _____)	**Personal protection** -chemoprophylaxis (specify___) -bednet -mosquito repellent or coil -None
	First Night YY/MM/DD	**Last Night YY/MM/DD**		
a.				
b.				
c.				
d.				
e.				

Outside of Swaziland								
Country	**Province / Town**	**Duration of Stay**		**Reason for sleeping away from current residence:** -previous residence -business -holiday -visiting friends/family -other (specify, _____)	**Personal protection** -chemoprophylaxis (specify___) -bednet -mosquito repellent or coil -None	**Means of travel** -Large bus -Kombi (van) -Personal car -Ride share (catch a ride/got a lift) -Airplane -Bicycle -Walked - other (specify, _____)	**Border Post of Re-Entry**	
		First Night YY/MM/DD	**Last Night YY/MM/DD**				- Lavumisa/Golela - Salitje/Onverwacht - Mahamba - Gege/Bothashoop - Sicunusa/Houtkop - Sandlane/Nerston - Ngwenya/Oshoek	- Bulembu/Josefsdal - Matsamo/Jeppe's Reef - Mananga - Lomahasha/Namaacha - Mhlumeni/Goba - Matsapha International Airport - Other
a.								
b.								
c.								
d.								
e.								

13. *Comments or* any other information that is relevant?

_____
_____

14. RDT result:☐positive ☐ negative ☐ not done

    If positive, patient referred to local health facility ☐ Yes ☐ No

    If no, why?

    _____
    _____

    DBS collected ☐Yes ☐ No ☐ Not Done

    If DBS not done, why?☐ Patient refused ☐ Other _____

Thank you for our participation in this study.

Appendix Q. DP weight-based dosing guidelines

Body weight (kg)	Daily dose (mg)		Tablet strength and number of tablets per dose
	PQP	DHA	
5 to <7	80	10	½ x 160mg / 20mg tablet
7 to <13	160	20	1 x 160mg / 20mg tablet
13 to <24	320	40	1 x 320mg / 40mg tablet
24 to <36	640	80	2 x 320mg / 40mg tablets
36 to <75	960	120	3 x 320mg / 40mg tablets
75 to 100	1,280	160	4 x 320mg / 40mg tablets
>100	There are no data on which to base a dose recommendation in patients weighing >100kg.		

Appendix R. Modified DOT dosing schedule

Day 1 DOT only arm

	Day 1	Day 2	Day 3	Day 4	Day 5
Present all 3 days	Rx 1 (DOT)	Rx 2 (self-admin)	Rx 3 (self-admin)		
Absent day 1		Rx 1 (DOT)	Rx 2 (self-admin)	Rx 3 (self-admin)	
Absent days 1 & 2			Rx 1 (DOT)	Rx 2 (self-admin)	Rx 3 (self-admin)

If needed to improve coverage, study staff will visit neighborhoods on Days 2 and 3. On these days, they may document that the dose that day was taken, remind subjects to take their medication, or directly observe ingestion.

Appendix S. Serious adverse event report form

To *be completed by Study Physician*

MINISTRY OF HEALTH

Adverse Drug Reactions (ADR) Report Form

Report can be returned to Central Medical Stores by fax 25186279 or 25186642
Email swazilandpharmacovigilance@gmail.com or cms@ealnet.co.sz or
Post to: Adverse Drug Reaction, Central Medical Stores, P. O Box 72, Kwaluseni
For Further inquiries, please contact the Pharmacist (Pharmacovigilance) at Central Medical Stores at 25184111 or 25187255

Section (A): Patient Information

Patient initials or ref. no.: ----------Sex: ☐ M ☐ F Pregnant? No ☐ Yes ☐ Unknown ☐
Weight (if known): _____kg Date of birth: (dd/ mm/ yyyy) / / or age (at last birthday):_____

Section (B): Medication History

All Drug Therapies/ Vaccines Prior to ADR (Please use trade names and circle the suspected drug.)	**Batch number**	**Daily Dosage**	**Route**	**Date Begun**	**Date Stopped**	**Indication for Use**

Allergies or other relevant history (including medical history, liver/ kidney problems, smoking, alcohol use etc)
_____

Section (C): About the Adverse Drug Reaction

Date of onset of ADR (dd/ mm/ yyyy) / /
Description of event: ----------

Category of ADR (please tick)

☐ Suspect minor/ major reaction from a drug (e.g. allergic reaction)
☐ Adverse Event (e.g. congenital defects)
☐ Product Use Error (e.g. use of antibiotic instead of NSAID)

Severity (can tick more than one if appropriate):

☐ Life threatening
☐ Hospitalized (dd/ mm/ yyyy) / /
☐ Hospitalization NOT required

Relevent Laboratory result:_____

Section (D): Treatment & Outcome

Treatment of ADR: □ No □ Yes. Details (including dosage, frequency, route, duration) ----------
---

Outcome:
□ Recovered on: (dd/mm/yyyy) / /
□ Not yet recovered
□ Unknown
□ Died on: (dd/mm/yyyy) / /
□ Persistent disability
□ Birth defect
□ Medically significant events
Details: _____

Section (E): Reporter Details
Name:_____ Sector of service: _ Private _Public
Occupation: _Doctor _Dentist _Pharmacist _Nurse _Others_____
Correspondence Address:_____
Tel. no.: _____Fax. no.: _____Email: _____
Also report to: _Manufacturer _Distributor/Importer _Others_____ Date of this report:_____

FOR OFFICIAL USE ONLY

Report to: Manufacturer □ Distributor/Importer □ Other □_____

Reported by: _____ Capacity_____

Instructions/ Notes

1. ADR can be briefly described as a noxious and unintended response to a drug or vaccine when the normal dose is used.
2. This report form is used for voluntary reporting of all suspected ADR.
3. There is no need to put down the full name of the patient.
4. Please provide information to every section. Information of individual reporter will be treated with strict confidence.
5. Please use another page for additional information if necessary.
6. Where date is required write in this format DDMMYYYY

"Completion of this form is not an admission of guilt or negligence"

Additional questions (also completed by study physician):

20) Maximum severity (See WHO Grading) |_|_|
    1=Mild, 2=Moderate, 3=Severe, 4=Life-threatening
21) Suspected relationship |_|_|
    0=None, 1=Unlikely, 2=Possible, 3=Probable, 4=Definite
22) If the event occurred in association with medication, was the event listed on the medication package insert? |_|_|
    1=Yes, 2=No, 3=N/A

Appendix T.WHO Grading for Determining Severity of Adverse Events

Appendix: WHO TOXICITY GRADING SCALE FOR DETERMINING THE SEVERITY OF ADVERSE EVENTS

WHO Toxicity Grading Scale for Determining The Severity of Adverse Events

HEMATOLOGY				
ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
Hemoglobin	9.5 - 10.5 gm/Dl	8.0 - 9.4 gm/Dl	6.5 - 7.9 gm/Dl	< 6.5 gm/Dl
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75000-99000/mm^3	50000-74999/mm^3	20000-49000/mm^3	<20000/mm^3
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Fibrinogen	0.75 - 0.99 X LLN	0.50 - 0.74 x LLN	0.25 - 0.49 x LLN	< 0.25 x LLN
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Methemoglobin	5 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20 %
LIVER ENZYMES				
AST (SGOT)	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
ALT (SGPT)	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
GGT	1.25 -2.5 x ULN	1.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Alkaline Phosphatase	1.25 - 2. 5 x ULN	1.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
CHEMISTRIES				
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 or mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement Rx required or hospitalization required.	< 2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or mental status changes or coma

Appendix: WHO TOXICITY GRADING SCALE FOR DETERMINING THE SEVERITY OF ADVERSE EVENTS

CHEMISTRIES (continued)				
Hyperglycemia (note if fasting)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL life-threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive Rx or hospitalization required	< 1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	1.1 - 1.5 x ULN	1.6 - 2.5 x ULN	2.6 - 5 x ULN	> 5 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Creatinine	1.1 x 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or required dialysis
URINALYSIS				
Proteinuria	1+ or < 0.3% or <3g/L or 200 mg - 1 gm loss/day	2 -3 + or 0.3 - 1.0% or 3-10 g/L 1- 2 gm loss/day	4+ or > 1.0% or > 10 g/L 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only	gross, no clots	gross+ clots	obstructive or required transfusion
CARDIAC DYSFUNCTION				
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; No Rx required	requires treatment
Hypertension	transient inc. > 20 mm; no Rx	recurrent, chronic, > 20 mm, Rx required	requires acute Rx; No hospitalization	requires hospitalization
Hypotension	transient orthostatic hypotension, No Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

Appendix U. Acceptability Assessment: Adult Informed Consent Form

(Focus Group Discussions with Study Participants or the Malaria Surveillance Team)

Introduction

Greetings! My name is _____. I would like to invite you to participate in a group discussion that is part of a research study about the acceptability of methods to eliminate malaria in the community. The study is organized by the National Malaria Control Program (NMCP) within the Ministry of Health. Your participation is important, although entirely voluntary. Please take your time to make your decision about participating, and discuss your decision with your family and friends if you wish. If you have any questions, you may ask me. Funding for this study is provided by the Bill & Melinda Gates Foundation.

Why am I being asked to be a part of this study?

- *If a TPE community member who participated in the study intervention:* You took part in a malaria elimination intervention 4 to 10 days ago and we would like to hear your impressions about malaria and the malaria intervention that was conducted.

- *If a member of the malaria surveillance team:* You have been part of the malaria surveillance team since the beginning of the study. In this capacity, you can provide us with valuable insight about the community's perspectives on malaria and the malaria intervention that was conducted.

Why is this study being done?

The purpose of this study is to understand the experience with malaria 'screening and treatment' or 'treatment without screening' of residents who live within 500 meters of a confirmed malaria case. Communities have been selected at random to receive one of these two interventions. Specifically, we are interested in your experience with the malaria intervention offered to you after a malaria case was been identified in your community.

How many people will take part in this study?

If a TPE community member: About 150 people will take part in this study.
If a member of the surveillance team: The entire surveillance team will be invited to participate.
.

What will happen if I take part in this research study? *(NOTE TO STUDY STAFF: CIRCLE ONE OF THE BELOW)*

- *For Focus Group Discussions with TPE Study Participants:* I will conduct a group interview with you and your family and or neighbors in either the local health facility or at a location near your home. I will ask you to describe your experiences with the study intervention. Specifically, I will ask how your participation in the intervention affected you and or your family and community.

- *For Focus Group Discussions with the Malaria Surveillance Team:* I will conduct a group interview with you and other members of the malaria surveillance team. I will ask you to describe your experiences offering the study interventions to the community.

I will make a sound recording of our conversation. After the group discussion, someone will type into a computer a transcription of what is on the tape and will remove any mention of names. The sound recording will then be destroyed.

How long will I be in the study?

Participation in the study will take a total of 1 hour.

Can I stop being in the study?

Yes, you can decide to stop at any time. Just tell me or the study staff right away if you wish to stop being in the study. Also, I may stop you from taking part in the study at any time if I believe it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What risk can I expect from being in the study?

Some of the interview questions may make you uncomfortable. [For focus group interviews: There is a risk that other focus group members may mention that you participated in this study or may repeat what you said in the group to others outside of the group.] You are free to decline to answer any questions you do not wish to answer and we will not collect any names or personal identifiers during the interviews.

Are there benefits to taking part in the study?

There will be no direct benefit to you from participating in this study. However, the information that you provide may help the National Malaria Control Program better understand how to find and treat malaria cases in your community.

What other choices do I have if I do not take part in the study?

You are free to choose not to participate in the study. If you decide not to take part in the study, there will be no penalty to you.

Will information from the records be kept private?

We will not inform anyone of your participation in the study and your name will be removed from the transcribed recordings and the tape recordings will be destroyed. The researchers will ask you not to say your name or other identifying information during the interview. Organizations that will examine the data are the National Malaria Control Program in Manzini, Swaziland, the Clinton Health Access Initiative in Mbabane, Swaziland and the University of California San Francisco, United States of America. Your name will not appear in any reports or publications.

What are the costs of taking part in this study?

You will not be charged for any of the study procedures.

Will I be paid for taking part in this study?

You will not be paid for taking part in this study.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you in any way.

Who can answer my questions about the study?
You can talk to the researcher about any questions, concerns, or complaints you have about this study during your interview. If you have any questions about this study or your participation, you can contact our Study Coordinator at +268 #### ####. If you wish to voice any problems or concerns you may have about how this study is being conducted, please call the office of the Swaziland Ministry of Health's Ethics Committee at +268 2404 7253.

CONSENT
You have been given a copy of this consent form to keep. PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to be in this study, or to withdraw from it at any point without penalty or loss of benefits to which you are otherwise entitled. If you wish to participate in this study, you should sign below.

Date	Name	Signature or finger print

Date	Name of Person Obtaining Consent	Signature of Person Obtaining Consent

WITNESS (only necessary if consent conducted in language other than English or SiSwati)
I witness that this consent form has been read to the participant in the language recorded below, and the participant has agreed to enroll in the study.
Language that consent was conducted in:_____.

Date	Name	Signature or finger print of witness

Appendix V. Qualitative questionnaires for the Acceptability Assessment – Individual Interviews with Refusers

Barcode: _____
Auto populate this field as this questionnaire will be triggered by individual refusing to participate in RACD/TPE individual level questionnaire. Grey-out (disable) so Agent cannot make changes.

Capture GPS Coordinates: Latitude (_____) Longitude (_____)
Distance from index case: _____
Auto populate this field, after Surveillance Agent captures GPS coordinates, tablet should calculate distance from index case by comparing with GPS coordinates of index case

Study arm (select one): ☐ RACD ☐ TPE

Participant age: _____
Auto-populate based on information collected from household level questionnaire

Participant gender: _____
Auto-populate based on information collected from household level questionnaire

Participant occupation (drop down list)

☐Student	☐Child or minor but not a student	☐Unemployed
☐Farming/Agriculture	☐Manufacturing/Factory	☐Other Manual Labor
☐Small-market sales or trade	☐Office or Clerical Work	☐Other (specify _____)

Surveillance Agent Name, check all that apply
☐Calsile ☐Sandile ☐Khaya ☐Mathokoza ☐Mduduzi ☐Mukelwe ☐Nombuso
☐Nomcebo ☐Nolwazi ☐Senzo ☐Thulani ☐Fanele ☐ Other_____

Thank you for answering a few questions for us. These questions will take approximately 5-10 minutes to answer. Your information will help us design interventions that are best for the community in future work to eliminate malaria.

- Do you mind telling me what your concerns are about participating in this intervention?
  _____
- Have you ever been part of a malaria screening before? ☐ Yes ☐No
  - If yes, when? _____ (*calendar pop up*)
- Have you ever refused to take part in a malaria screening in the past? ☐ Yes ☐No
  - If yes, why did you refuse?_____
- If you have been part of a malaria screening in the past (before this study), did you test positive for malaria? ☐ Yes ☐No
  - If yes, did you take medication? ☐ Yes ☐No
- Has anything in the past with medication influenced your decision not to participate in the intervention? ☐ Yes ☐No
  - If yes, what was the problem?_____
- Have you previously had malaria? ☐ Yes ☐No
- If yes, when was the last time you had malaria? _____yrs _____ months ____ days
- Were you informed about the intervention before the malaria nurses visited your household? ☐ Yes ☐No
  - If yes, how did that information influence your decision to refuse?

_____

- If you were not informed earlier, how did the information you received on the day of the intervention influence your decision to refuse?

_____

- Is there anything that would make you decide differently in the future?

_____

- What do you think is the best way to get rid of malaria in Swaziland?

_____

<u>Appendix W</u>. – Qualitative questionnaires for the Acceptability Assessment – Focus Groups with TPE Participants

Semi-structured interview guide

Focus Group ID #_____

Number of participants: _____

Total number of women: _____

Total number of men: _____

Participant age range: _____

List of participant occupations: _____

Previous participant in this clinical trial? ☐ YES ☐ NO

Date of interview _____

Start time _____End time_____

Initials of interviewer _____

Signed informed consent: ☐

These questions are loosely structured and meant to explore why community members choose to opt in or out of the clinical trial. The focus group discussion is intended to be 60 minutes. The researcher leading the focus group will describe the session, what topics will be discussed, expectations of member participation, and explain informed consent. Each participant will have to sign an individual informed consent that includes demographic information on a separate document. The demographic information and names will not be made public and are for the purpose of ensuring diversity in the focus group.

I. Background and experience with malaria, perception of risk in the community

- How many of you have lived in this community for at least 5 years? If you have not, where else have you lived?
- How many of you have had malaria in the last 5 years?
- Has the number of times you have had malaria changed in those 5 years? If yes, how?
- If you have had malaria, were you tested? If not, why not?
- If you were tested and the test was negative, did you take medication?
- What about medication for malaria? Tell me about your experiences taking medication for malaria. What kinds, what happened, where did you obtain it?
- Do you know other people who have had malaria, other than the index case in this screening study? If yes, what is your relationship to them?
- Do you think you are at risk for malaria? Why or why not?
- Who do you think is at risk for malaria? What should they do to protect themselves?
- Do you sleep under a bed net? Why or why not? Tell me more about how you feel about a bed net. Do you think it works? What are some of the problems, if any, you have experienced with your bed net?
- What else do you do to prevent malaria?

II. What experiences will most influence community uptake of the intervention?

These questions refer to any experiences in the past with malaria screening, NOT the focus group members experience during this clinical trial

- Have you ever been part of the NMCPs screening for malaria in affected communities? (If no, STOP, ask whether they have refused in the past or not had the opportunity to be part of a screening and then go to questions about experience during this clinical trial) If YES, continue with other questions.
- When did you participate in screening? How was your experience with the screening test done by the NMCP officers?
- Did you know when you were tested that an index case (your family member or neighbor) was suffering from malaria? If yes, do you know if the index case was a family member or neighbor?
- How far from the index case did you live? What do you think were the reasons your family member or neighbor (index case) got malaria?
- Do you think you were at risk since someone living near you got malaria? How about the risk for your family members?
- Are there people in your household you believe are at greater risk for malaria? Why or why not?
- If you have been part of a malaria screening in the past (before this study), did you test positive for malaria? Did you believe the test results? Why or why not?
- Are you aware of people in your area who have been screened or tested for malaria before? Please share their experiences with me if they did inform you.

*These questions refer to your experience during **this** clinical trial:

- Tell me about this malaria screening. How were you contacted? Who did you speak to and what was the message they gave you?
- What or who made you decide to participate? Tell me about your decision to be part of the screening.
- Are there other times or circumstances when you might decide not to accept medication if you have not been tested for malaria first?
- Do you feel differently or make different decisions about giving medication to your children? How?
- How did you learn about this intervention? Tell me what you thought when you first heard of it.
- Tell me about the time of day when you were contacted about the intervention, if you were home or work or elsewhere? Were you with family members? How far from the index case do you live?
- Why do you think your family member or neighbor (index case) got malaria? Do you think you are at risk since someone living near you got malaria? How about anyone in your family?
- Are there people in your village who you believe are at greater risk for malaria? Why or why not?
- Is this the first time you took malaria medication without being tested first? Would you do it again?
- What do you think about getting tested for malaria before you take medication? Is it important? Why or why not? Do you always get a malaria test when you have a fever? Why or why not? What do you do when the test is negative?
- Would you encourage others in your area to accept treatment before the start of the malaria season as prevention for malaria?

III. Impact of the intervention on daily life

- Have you ever taken malaria medication before?
- If yes, how did malaria medication make you feel after taking it? Were there any uncomfortable side effects? If yes, what were they?
- How about any other medications for malaria? If yes, how was it the same or different from this one?
- Would you take this medication again? Why or why not?
- Did you finish your medication? Why or why not?
- If medication was not finished, please explain why you didn't finish your medication.
- Do you think you can have malaria but not have symptoms?
- Do you think people should be tested before they take malaria medication? Why or why not?
- Do you believe giving malaria medication to everyone living near someone who has tested positive for malaria is a good way to get rid of malaria in Swaziland? Why or why not?

FOR ALL PARTICIPANTS IN THE QUAL STUDY:

- Do you have any other suggestions on how the NMCP can keep you informed and protected from malaria?
- What do you think is the best way to completely eliminate malaria in Swaziland?

Appendix X. Qualitative questionnaires for the Acceptability Assessment – Focus Groups with Malaria Surveillance Team (RACD & TPE Arms)

Semi-structured interview guide

Study participant ID #_____

Participant age: _____

Participant sex: _____

Date of interview _____

Start time _____End time_____

Initials of interviewer _____

Signed informed consent: ☐

- What is your overall opinion of this study?
- Do you feel that one of these interventions may be better than the other? If yes, how? If not, why not?
- How does offering TPE affect your job? Is it more or less difficult to implement than RACD? Describe how one intervention differs from the other in terms of implementation
- What do you think is working well? Please elaborate.
- What should be changed in terms of offering the interventions? Please elaborate.
- What do you think should be scaled up? Why?
- What do you think should be scaled back? Why?
- What sort of barriers did you encounter during your involvement with the study? Please describe them, particularly with whom you encountered barriers. (after 1st FGD, ask if this has changed over time and if so, how)
- Were there any particular groups who did not want to participate? Who and why?
- Why do you think those barriers were present?
- How do you think those barriers could be addressed?
- Did you do anything to overcome those barriers? If yes, what did you do?
- Were there any particular groups that were receptive to the interventions? Who and why? (after 1st FGD, ask if this has changed over time and if so, how)
- What effect do you think this study is having the community? Please elaborate. Do you notice a change in the effect over time?
- Do you think the community members you encounter understand this study and why it is being done?
- What do you think will define success in this trial?
- Is there anything else you would like to add?

Appendix Y. Swaziland Malaria Elimination Advisory Group (SMEAG)

Swaziland Malaria Elimination Advisory Group (SMEAG)
Terms of Reference

Swaziland Ministry of Health
National Malaria Control Program
June 2010

Background
In 2007, the Swaziland government established the goal of malaria elimination by 2015 in alignment with the Southern African Development Community (SADC) vision of a malaria-free southern Africa. Since then, the National Malaria Control Program (NMCP), along with its key technical and implementation partners, has mobilized resources to fund an elimination campaign, strategically planned the implementation of key elimination interventions, and begun to implement critical components of the elimination program. Major areas of focus include strengthening malaria diagnosis, establishing an active surveillance program, scaling up vector control coverage, expanding a health promotion campaign, and increasing monitoring and evaluation (M&E) activities.

Purpose
As Swaziland continues to target its goal of malaria elimination, the NMCP and its implementing partners require additional technical support and guidance to assure steady progress toward elimination. The Swaziland Malaria Elimination Advisory Group (SMEAG) is established to serve this purpose – to establish policy, to provide technical guidance on implementation of policies, and to monitor policy implementation and progress toward elimination.

Responsibilities
The Swaziland Malaria Elimination Advisory Group (SMEAG) has three major responsibilities.

1. Policy Establishment – The SMEAG meets regularly to review malaria elimination policies in surveillance, case management, and vector control and prevention. Where applicable, the group provides recommendations to the Ministry of Health on new policies and revision of existing policies. As the members of SMEAG are experts in their respective fields, they base policy recommendations on current research and regional and global best practices.

2. Technical Support and Guidance for Implementation – In addition to recommending malaria policy changes, SMEAG is responsible for providing regular support and guidance to the NMCP and its partners on technical issues related to implementation of policies or interventions. The SMEAG works with the NMCP and its partners to identify key challenges and bottlenecks, discuss solutions, and offer recommendations on overcoming impediments to elimination. Identified challenges are reviewed on a regular basis to ensure effective resolution of all issues.

3. Monitoring and Evaluation of Progress Toward Elimination –The SMEAG regularly reviews M&E indicators on the implementation of malaria policies and Swaziland's progress toward elimination. When necessary, the SMEAG recommends reorientation in policies, practices, and interventions to the NMCP and partners to ensure achievement of Swaziland's elimination goal.

Organization
SMEAG is composed of a general committee as well as four sub-committees in surveillance, case management, vector control and prevention. A global technical advisory committee, composed on regional and global experts on malaria elimination, provides additional remote technical assistance.
SMEAG General Committee

Chairperson: Rejoice Nkambule, Deputy Director of Health Services – Public Health
NMCP Secretariat: Simon Kunene, NMCP, Program Manager

- The Swaziland Ministry of Health, including the Directorate of Health Services and the National Malaria Control Program (NMCP)
- The World Health Organization (WHO)
- United Nations Children's Fund (UNICEF)
- The Southern Africa Malaria Elimination Support Team (SAMEST) – a collaboration between the Clinton Health Access Initiative (CHAI) and the Global Health Group (GHG) of the University of California – San Francisco (UCSF)
- The Swaziland National Association
- The Swaziland Medical and Dental Association
- Swaziland Nurses Association
- Red Cross
- Traditional Healers Organization
- University of Swaziland (UNISWA)
- Chairpersons from each subcommittees

Sub-Committees

1. SURVEILLANCE SUBCOMMITTEE –
Chairperson: Nhlanhla Nhlabatsi, Epidemiology Unit, Ministry of Health
NMCP Secretariat: Zulisile Zulu, Nyasatu, Sabelo Dlamini, Bongani Dlamini

- Meteorological Services, Ministry of Works
- Department of Immigration, Ministry of Home Affairs
- Health Management Information Systems (HMIS), Ministry of Health
- Epidemic Preparedness and Response (EPR), Ministry of Health
- Epidemiology Unit, Ministry of Health

2. CASE MANAGEMENT SUBCOMMITTEE –
Chairperson: Doctor from Good Shepherd Hospital
NMCP Secretariat: Nolwazi Sibusani, Sarah Adra-Dartey, Steven Mthethwa

- Nurse matrons from major hospitals and health centers
- Doctor representatives from major hospitals and health centers
- Pharmacy Department, Ministry of Health
- National Laboratory Services, Ministry of Health
- Swaziland Medical and Dental Association

3. VECTOR CONTROL AND PREVENTION SUBCOMMITTEE –
Chairperson: Edmund Dlamini, Principal Health Inspector, Ministry of Health
NMCP Secretariat: Quinton Dlamini, Zandie Dlamini

- Environmental Science Department, UNISWA
- Entomology Department, UNISWA
- Ministry of Agriculture
- Environmental Health, Ministry of Health
- Environmental Authority, Ministry of Health

4. HEALTH PROMOTION SUBCOMMITTEE –
Chairperson: Nokuthula Mahlalela, Senior Health Educator, Ministry of Health
NMCP Secretariat: Teclar Maphosa, Mancoba Mabuza

- Health Promotion Unit, Ministry of Health
- Media Institutes of South Africa
- Department of Health Promotion, UNISWA
- Rural Health Motivator Program, Ministry of Health
- School Health Teams

Global Technical Advisory Committee

The Global Technical Advisory Committee is composed of global and regional experts in malaria elimination, epidemiology, case management, vector control, surveillance, health promotion, and M&E. These experts are drawn from regional and global academic and research institutions, UN agencies, NGOs, and other organizations.

Meetings and Deliverables

The SMEAG General Committee meets biannually in November and May (the beginning and end of the malaria season) to review policies, implementation of policies and interventions, and progress toward elimination. Meetings may include the following agenda topics.

1. Introduction
2. Review of minutes
3. Review of policies
    a. Surveillance
    b. Case management
    c. Vector control and prevention
4. Review of elimination policy and intervention implementation – review of key indicators, identification of key challenges, discussion of problems, and recommendations for implementation
    a. Surveillance
    b. Case management
    c. Vector control and prevention
    d. Health promotion
    e. Project management and M&E
5. Evaluation of progress toward elimination
6. Conclusion

The SMEAG Subcommittees meet biannually prior to the meeting of the General Committee (and more frequently if needed) to identify issues and discuss preliminary solutions, which then are presented to the general committee. The Global Technical Advisory Committee provides ongoing support whenever requested by members of the General Committee or Sub-Committees.

At the conclusion of each meeting, the secretary of the meeting produces a set of minutes that include detailed account of all discussions and recommendations. After the meetings, the NMCP and relevant partners will then incorporate recommendations into existing work plans.

Appendix Z. TPE Safety Monitoring Committee

Terms of Reference (TOR)
Targeted Parasite Elimination (TPE) Pharmacovigilance and Adverse Drug Reactions Committee
(**Data and Safety Monitoring Committee)**
for approval at December 2014, Committee Meeting

This TOR provides the framework for the responsibilities and activities of the Targeted Parasite Elimination Pharmacovigilance and Adverse Drug Reactions Committee (Data and Safety Monitoring Committee). The committee shall oversee the safety of the study drug – dihydroartemisinin-piperaquine (DP) or artemether-lumefantrine (AL) as an alternative to DP, and shall perform this function by receiving and reviewing all data on DP or AL administered to study participants and by providing appropriate advice to the Ministry of Health which includes the National Malaria Control Program (NMCP) and the Swaziland Ethics Committee (SEC).

1. Background and scope of the Committee

Swaziland is currently aiming for malaria elimination by 2015. A major part of the approach has been reactive case detection (RACD), or the testing of individuals around index cases as a way to identify and treat secondary infections. Although the approach is useful for finding infected individuals and hotspots, there are some technical and logistical challenges relating to the test and treat approach. Presumptive treatment without testing, also known as targeted parasite elimination (TPE), has potential to be more effective and feasible. The goal of TPE is to critically evaluate this approach versus RACD as a surveillance and response strategy for malaria elimination in Swaziland. The TPE Pharmacovigilance and Adverse Drug Reactions Committee Committee was established in December 2014 to monitor the safe use of DP or AL in the study. Members of the committee are representatives of institutions overseeing pharmacovigilance and adverse drug reactions in Swaziland. The committee includes individuals from the Swaziland Malaria Elimination Advisory Group (General Committee), the Ministry of Health (pharmacovigilance), the World Health Organization (WHO) and non-governmental organizations such as Management Sciences for Health (MSH).

2. Roles and Responsibilities

The purpose of the committee is to provide drug safety surveillance for the use of DP or AL in TPE in Swaziland. The committee will 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to the study investigators concerning the continuation, modification, or termination of the study. The committee will consider study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

The Committee is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, and voting procedures prior to initiating any data review. The Committee is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The Committee will review the protocol for any major concern prior to implementation. During the trial, the Committee should review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. As part of this responsibility, Committee members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants. The Committee should also assess the performance of overall study operations and any other relevant issues.

3. Membership of the Monitoring Committee

Members of the committee will be comprised of staff from the Ministry of Health and its partners conversant on drug safety and field drug studies and will be from the following institutions

- The Swaziland Ministry of Health – Central Medical Stores
- The Swaziland Ministry of Health – Scientific and Ethics Committee
- Measurement Sciences for Health (MSH)
- World Health Organization (WHO)

Each institution will be represented by one member, and one or more observers invited should there be need. Members will include experts in statistics, epidemiology, clinical trial design, and include at least one local clinician. Core members should have decision-making power from their institution as well as good knowledge of drug safety and random control trial research studies. In case of decisions to be made by the committee, which are not agreed by unanimity, core

members will vote for the majority. Other institutions and members to the committee may be added as seen fit by the committee.

Minutes from the committee meetings will be made available for review to the group. The committee will be led by a Chairperson and Secretary whose functions are briefly outlined below:

Chairperson: The chair position will be assigned by vote among committee members at the inaugural meeting and revisited each year.

Secretary: The secretary position will be assigned by vote among committee members at the inaugural meeting and revisited each year. The secretary will be responsible for arranging the committee meetings, including agenda and recording and sharing minutes.

4. Meetings

An initial meeting will be held in December 2014 to introduce the project to committee members. Following this introductory meeting, the committee will meet every quarter or more frequently if required. These meetings will be planned around observed and regular reports of suspected adverse drug reactions. Committee members are expected to attend meetings 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. However, the busy schedules of members will be respected and meetings convened their availability. Depending on the agenda, independent advisors or experts can be invited to the meeting, upon approval by the chair and secretary.

5. Terms of Service

Committee members will be invited to commit to two years of service. If a member is unable to meet the terms of membership, another member of that institution may be nominated with the approval of committee members.