A mixed-method operational research study on the use of tafenoquine and G6PD testing for radical cure of *Plasmodium vivax* malaria in passive and active case detection in Vietnam

1 Study summary

Protocol identifying number: MMV_TQ_Vietnam_2201

Version Number and Date: Version 4.0; 10 April 2025

Name and address of funder:

Unitaid, Global Health Campus, Chemin de Pommier 40, 5th Floor, 1218 Grand-Saconnex, Switzerland.

Bill and Melinda Gates Foundation (BMGF), Seattle, USA

Name and address of the sponsor[1]: PATH, 11th floor, Hanoi Tower, No 49, Hai Ba Trung street, Hoan Kiem district, Ha Noi, Viet Nam

Name, title and contact (including phone number) of the sponsor medical lead: Dr. Nhu Nguyen, GHS and Malaria Vietnam Program Director, PATH, nnguyen2@path.org, +84 28 3520 2912

Name, title, affiliation and contact (including phone number) of the Principal Investigator: Dr Bui Quang Phuc; Head of the Treatment and Clinical research at National Institute of Malariology, Parasitology and Entomology, phucnimpe@gmail.com , +84 983522874

Name and address of the sponsor delegate(s)/implementing partner(s): National Institute of Malariology, Parasitology and Entomology (NIMPE), 34 Trung Van street, Nam Tu Liem district, Ha Noi, Viet Nam

Total budget: From Government budget for Science and Technology: 0 VND
From PATH: Approximately 5.8 billion VND (~246.800 USD)

[1] Study sponsor as defined by ICH GCP E6(R2)

Sponsor signature

I herewith approve the following protocol entitled "**A mixed-method operational research study on the use of tafenoquine and G6PD testing for radical cure of *Plasmodium vivax* malaria in passive and active case detection in Vietnam**", Version 4.0, 10 April 2025

Signature	Signed by: Nguyen To Nhu B2F508CEECCB4E3...
Name	Dr. Nhu Nguyen
Role	EPR and Malaria Vietnam Program Director, Sponsor Medical Lead
Date	May 11, 2025

Study Aim	The primary aim of the study is to assess whether the use of tafenoquine after semi-quantitative G6PD testing for radical cure of *Plasmodium vivax* malaria is operationally feasible based on the revised algorithm in Vietnam, a country approaching elimination.	
Summary	This is a prospective mixed-methods operational feasibility study with the primary aim of assessing the operational feasibility and secondary aim of assessing the safety, acceptability and cost of a revised treatment algorithm for *P. vivax* malaria that includes point-of-care semi-quantitative G6PD testing and radical cure (RC) with tafenoquine (TQ). This study will involve introduction of the revised algorithm with G6PD testing and radical cure drugs in health facilities in 7 districts as well as into active (test and treat) and reactive case finding strategies. The differences between integrating G6PD testing and TQ into active, reactive, and passive case finding strategies in terms of effectiveness and cost is expected to be part of the evidence generated by this study and all relevant study endpoints will be stratified by case finding strategy where possible. This study will use mixed methods, including the quantitative assessments of case management data, qualitative assessments (including interviews, focus group discussions), and a costing component that compares costs across case-finding strategies. Intervention safety will be measured through a follow-up visit of patients to identify, manage, and assess any instances of acute hemolytic anemia and moderate, severe, or serious adverse events. The study population will include *P. vivax* patients, health care providers that manage vivax patients as well as malaria program staff responsible for active case detection.	
Implementation Package	The implementation package includes the following interventions - Application of a new *P. vivax* treatment algorithm that incorporates new test and treatment for radical cure (G6PD test + TQ) and deployment strategies as part of active case detection - The training of health care providers and malaria program staff in the new algorithm and the use of the new test and treatment for radical cure - Patient counselling - Strengthening follow-up visits for study patients - Quality monitoring of *P. vivax* case management Accompanying supporting measures: job aids, work instructions and strengthening of supervision and pharmacovigilance (PV) processes	
Study design	<u>Category of research: implementation research</u> <u>Design</u>: prospective longitudinal study with the introduction of intervention (TQ after G6PD testing) in selected health facilities, interviews and group discussions <u>Mixed-methods approach:</u> qualitative component, quantitative component, , and costing component	
Study Objectives and Endpoints (select endpoints included, see full list table 4)	**<u>Primary objective:</u>** 1. Assess adherence to a revised case management including both TQ and PQ for *P. vivax* malaria	**<u>Primary endpoint</u>**: 1.1 Proportion of *P. vivax* infected individuals that are correctly treated with TQ based on the revised algorithm as an aggregate and within each of three case finding strategies. 1.2 Proportion of *P. vivax* and mixed *P. vivax* infected individuals that are correctly treated with PQ based on the revised

		algorithm as an aggregate and within each of three case finding strategies.
	Secondary objectives: 2. Determine the capacity of the health system to safely implement RC after G6PD testing in different case finding strategies	**Secondary endpoints**: 2.1 Proportion of non-eligible patients that receive RC 2.2 Proportion of patients experiencing acute hemolytic anemia (AHA) during the patient follow-up period
	3. Assess the quality and effectiveness of training and supervision strategies through competency testing, and training and supervision evaluations	3 Health care provider knowledge and skills regarding G6PD testing and RC over time as determined by a competency assessment
	4. Explore barriers and facilitators to adding TQ to the treatment algorithm within different case finding strategies	44 Patients, health care provider and supervisors' perceptions of and experience with the new RC algorithm, specifically TQ, as reported in interviews and focus group discussions
	5. Determine the costs associated with introducing a single dose RC.	5.1 Total monetary cost of including G6PD testing and single dose cure compared across case finding strategies 5.2 Per patient monetary cost of including G6PD testing and single dose cure compared across case finding strategies.
	6. Monitor the frequency of recurrences in study participants	6.1 Number of recurrences of *P.vivax* identified by study participants until Day 29, in total and stratified by treatment type.
	7. Monitor Serious Adverse Events (SAE) in study *P.vivax* patients receiving RC	7.1. Number of *P. vivax* patients reporting serious adverse events after TQ and PQ administration until Day 29. 7.2. Frequency and severity of each serious adverse event reported after TQ and PQ administration during until Day 29.
	Exploratory objectives: 1. Monitor moderate and severe adverse events in study *P.vivax* patients receiving RC	**Exploratory endpoints:** 1.1 Number of *P. vivax* patients reporting moderate and severe adverse events after TQ and PQ administration until Day 29.

		1.2. Frequency and severity of each moderate and severe adverse event reported after TQ and PQ administration until Day 29.
Methods:	Quantitative component – Adherence and safety measures to be computed based on individual patient's case management outcomes – Training evaluation using competency testing and training satisfaction questionnaire – Monitoring new patient infections to be computed based on individual patient case management outcomes as well as national surveillance data Qualitative component Focus Group Discussions and In-depth Interviews Costing component Standardized cost data-collection instruments will be used	
Target population	Health care providers (HCP) directly involved in the management of *P. vivax* patients Patients with confirmed *P. vivax* infection or mixed *P.vivax* infections Other health professionals indirectly involved in management of vivax patients (qualitative component)	
Sampling strategy and target sample size	Health facilities (12 to 36) are selected purposively taking into consideration factors that will maximize sample size and that are representative of health facilities managing malaria. All health care providers who consent in target facilities and patients consented for study will be included. Based on historical *P. vivax* caseloads, we anticipate a minimum of approximately 10 patients to be enrolled per month of study implementation. A minimum of 30-40 patients would allow for estimating the endpoint for the primary objective with adequate precision. A maximum of 150 patients will be enrolled to allow for estimating the endpoint for the primary objective with greater precision. A minimum of 60 and maximum of 184 HCPs and malaria case management supervisors will also be enrolled. The minimum number of patients and HCPs assumes all sites are active for the entire duration of study enrollment.	
Selection criteria	Criteria for facility selection: Sufficient *P. vivax* cases; Accessibility (distance to the district hospital which can assess the severity and provide intensive care, and provincial hospital where blood transfusion and dialysis can be carried out); Alignment with current standard of care (existing G6PD tests); Functional referral system Criteria for HCP selection: All HCP involved in the treatment of vivax patients at selected facilities and as part of case finding activities and who agree to be part of the study Criteria for patients' selection: *P. vivax* confirmed patients from 6 months old and above who are treated at a participating HF or through case finding, who do not have signs of severe malaria upon admission and who agree to be part of the study	

Analysis	Quantitative analysis of case management data: Descriptive analysis of primary and secondary endpoints, stratified by type of case finding strategy where possible. Qualitative component: Deductive approach using content analysis, stratified by type of case finding strategy. Costing component: Descriptive cost analysis, stratified by type of case finding strategy.
Study implementation duration	A minimum of 4 months duration is anticipated

Protocol version	Changes from previous version	Sections of the protocol modified
3.0	Changes to the description of the current national malaria guidelines to reflect the adoption of a 7 day PQ regimen after WHO recommendations were adopted. Modifications to Figure 5.	5.4, 7.2.1 and 7.2.2.1 and Figure 5
4.0	Changes the “monitor the frequency of new malaria infections in study participants during study conduct” to “monitor recurrences in study participants until Day 29” Remove Day 90 visit due to the shortened study implementation period and the Day 90 follow-up visit was primarily for monitoring of additional malaria infections. Patients are still followed up for safety until Day 29. Reduce the minimum sample size from 60 to 30-40 due to the shortened enrollment period as well as the caseload in 2024 Minor modifications throughout the protocol to note the updated regulatory status of TQ, more current caseload data, and impacts on the study duration and sample size The interim analysis is removed throughout the protocol due to the shortened	Protocol synopsis, section 3.1 and section 8.8 Protocol synopsis, section 8.3 and section 10.2.6

	period of the study duration of 4-6 months.	

2 List of acronyms

Acronym	Definition
ACT	Artemisinin-based Combination Therapy
ACD	Active Case Detection
pACD	Pro-Active Case Detection
rACD	Reactive Active Case Detection
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHA	Acute Hemolytic Anemia
AL	Artemether-lumefantrine
bw	Body weight
CHS	Commune Health Station
CHW	Community Health Worker
CMO	Chief Medical Officer
CQ	Chloroquine
CST	Country Study Team
CRF	Case Report Form
DHC	District Health Center
FDA	Food and Drug Administration
FGD	Focus Group Discussion
G6PD	Glucose-6-Phosphate Dehydrogenase
G6PDd	G6PD deficient
G6PDi	G6PD intermediate
G6PDn	G6PD normal
GST	Global Study Team
HCP	Health Care Provider
HF	Health Facility
IAF	Informed Assent Form
ICF	Informed Consent Form
IDI	In-Depth Interview
IR	Implementation Research

ISOC	Independent Study Oversight Committee
IRB	Independent Review Board
LFU	Loss-to-Follow-Up
MMV	MMV Medicines for Malaria Venture
MoH	Ministry of Health
NIMPE	National Institute for Malariology, Parasitology and Entomology
PI	Principle Investigator
PCD	Passive Case Dectection
POC	Point-of-Care
PV	Pharmacovigilance
PQ	Primaquine
RAI3E	Regional Artemisinin Initiative 3 Elimination
RC	Radical Cure
RDT	Rapid Diagnostic Test
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRT	Safety Review Team
TGA	Therapeutic Goods Administration
TQ	Tafenoquine
VHW	Village Health Worker
WHO	World Health Organization
WHO ERC	World Health Organization Ethics Review Committee

3 Table of content

4 Study governance

4.1 Institutions involved in the study

The following organizations are involved in the planning, conduct and reporting of this study:

- NIMPE
- PATH
- MMV
- Unitaid
- BMGF

Unitaid and BMGF are providing funding for this study. MMV is the primary recipient of the 25 million USD grant, which is included under the umbrella of the Partnership for Vivax Elimination (PAVE) initiative, co-led by MMV and PATH. MMV is the sponsor of feasibility studies in Peru, while PATH with funding from Unitaid and BMGF is the sponsor of the feasibility studies in Ethiopia and in Vietnam. A close partnership has been established with the National Institute of Malariology, Parasitology and Entomology (NIMPE) and the Ministry of Health (MoH) at the central level and regional levels. The table below lists primary responsibilities of MMV, PATH, NIMPE and implementing partners.

Table 1: Roles and responsibilities of institutions involved in the study

	PATH	**National Institute of Malariology, Parasitology and Entomology (NIMPE)**	**Ministry of Health (MoH)**	**MMV**
Development of country-specific protocol and other study documents	R	R	C	C
Submission to local institutional review boards IRBs	C	R		C
Procurement of study supplies	R	R		I
Selection of study sites	C	R	C	I
Community Engagement	C	R	C	C
Study conduct	I	R		I
Patient safety monitoring	R	R	I	C
Data analysis	R	C	I	I

R=responsible, C= consulted, I=informed

4.2 Study Investigators

Table 2: List of study investigators

Name and title	**Position and Affiliation**
Dr. Bui Quang Phuc	Principal Investigator, Head of Malaria Treatment and Research, NIMPE
Dr. Hoang Dinh Canh	Co-Principal Investigator, Director of NIMPE.
Dr. Nguyen Van Hong	Data manager, vice Head of Malaria Treatment and Research, NIMPE
Dr. Nhu Nguyen	Co-Investigator, Malaria Program Director, PATH
Nguyen Thanh Huyen	Co- Investigator, Malaria Team Leader, PATH
Thang Tran	Co-Investigator, Senior Program Officer, PATH
Dr. Gonzalo Domingo	Co-Investigator, Scientific Director, PATH
Emily Gerth-Guyette	Co-Investigator, Program Officer, PATH

5 Background and study rationale

5.1 Background on global malaria burden, WHO treatment recommendations and existing diagnostics and treatments

Malaria is a major health problem in many countries of the world. Of the six parasite species that cause malaria in humans, *Plasmodium vivax* (*P. vivax*) is the second most common one, after *P. falciparum*, and has the largest geographic distribution (Gething et al., 2012). The World Health Organization (WHO) estimates the global *P. vivax* malaria burden at 6.4 million cases in 2019 (World Health Organization (WHO), 2020). *P. vivax* infection is characterized by the persistence of latent parasites (liver-stage hypnozoites), which cause recurrent malaria episodes months or even years after the initial infection (Imwong et al., 2007). The frequency and pattern of relapses varies geographically, with relapse rates generally ranging anywhere between 8% to 80% (Battle et al., 2014).

Effective prevention of relapses is crucial to reducing transmission and achieving vivax elimination (Commons et al., 2020; Ome-Kaius et al., 2019). WHO's guidelines for the treatment of *P. vivax* malaria recommend treatment of the blood stage infection and of the latent liver stage to prevent those relapses, onward transmission, and progression to severe disease (World Health Organization (WHO), 2021). This treatment approach is known as "radical cure" (RC).

Chloroquine (CQ) is the most widely used treatment for blood stage infection. In areas where CQ resistance is prevalent, artemisinin-based combination therapy (ACT) is recommended. The only radical cure drugs that can effectively treat the latent liver stage of *P. vivax* infections and prevent relapses are 8-aminoquinolines (8-AQ) (Baird et al., 2016). For over 60 years, primaquine (PQ) has been the only 8-AQ available for *P. vivax* malaria latent liver stage treatment. It is generally given as a 14-days course of 0.25mg/kg body weight (bw) per day. Recently, the WHO has also recommended a 7 day course of 0.5 mg/kg body weight (bw) per day.

However, the widespread and optimal use of PQ within national policies and routine practices has been variable (Recht et al., 2018). Due to the long treatment regimen, patients' adherence is proving challenging in many settings. In addition, concerns on the part of healthcare providers (HCP) as to the safety of 8-AQ treatment in the absence of a reliable point-of-care (POC) G6PD test has limited PQ use (Douglas et al., 2017; Takeuchi et al., 2010).

Tafenoquine (TQ) is another 8-AQ which was approved by the US Food and Drug Administration and the Australian Therapeutic Goods Administration (TGA) in 2018, as well as Regulatory Authorities in Brazil, Peru, Thailand, the Philippines and Colombia; and it was approved by Drug Administration of Vietnam in October 2024. TQ was evaluated in several studies, including a Dose and Efficacy Trial Evaluating Chloroquine and Tafenoquine in Vivax Elimination (DETECTIVE) (Lacerda et al., 2019; Llanos-Cuentas et al., 2014) and a Global Assessment of Tafenoquine Hemolytic Risk (GATHER) trial (Llanos-Cuentas et al., 2019). The DETECTIVE study was a randomized, phase 2b–3 trial investigating the efficacy of CQ plus TQ versus CQ plus placebo for the radical cure of *P. vivax* malaria in participants with phenotypically normal G6PD activity. An additional arm with CQ plus PQ was also analysed as benchmark.

The DETECTIVE study, conducted in 522 patients investigated a 1-day course of TQ (300mg), a 14-day course of PQ (15mg), or placebo, with all patients also receiving a 3-day course of CQ to treat clinical symptoms, met its primary endpoint. Using a confirmed FDA-preferred analysis (Kaplan Meier analysis), a significantly greater proportion of patients in the TQ group remained relapse-free over the 6-month follow-up period compared with patients in the placebo group (62.4% vs 27.7%), with an odds ratio of 0.3, $p<0.001$. Further, a significantly greater proportion of patients in the primaquine group were relapse-free over the 6-month follow-up period compared with patients on placebo (69.6% vs 27.7%), with an odds ratio of 0.26, $p<0.001$. High compliance with PQ treatment of greater than 95% was observed in this controlled clinical setting.

Adverse events from the study were consistent with the known safety profile of TQ. Mild, asymptomatic declines in hemoglobin (a protein in red blood cells that carries oxygen) were observed more frequently in patients taking TQ, and all recovered without intervention. The proportion of patients experiencing adverse events (AEs) in the first 29-days during the 6-month study was similar for each treatment group; the frequency was 48.8% for TQ, 46.5% for PQ, and 48.9% for placebo. The frequency of serious AEs was 8.1% for TQ (n=21, 14 of which were due to decline in hemoglobin that were all mild to moderate in severity and all recovered without specific medical intervention), 3.1% (n=4) for PQ and, 4.5% (n=6) for placebo.

GATHER was a randomized, controlled trial aimed to compare hemolytic risk but also efficacy among patients with normal G6PD enzyme activity. The GATHER study, conducted in 251 patients, investigated the effect of a single-dose of TQ (300mg) on levels of hemoglobin when compared to a 14-day course of PQ (15mg), with all patients also receiving a standard 3-day course of CQ.

The incidence of decline in hemoglobin (the primary endpoint) was very low and similar between the two treatment groups (2.4% for patients receiving TQ 1.2% for patients receiving PQ), with the difference in proportions (95% CI) of 1.23% (-4.16%, 4.98%).

The frequency of adverse events was 72% for the TQ group and 75% for the PQ group and the frequency of serious adverse events was 4% for the TQ group and 1% for the PQ group.

Some data from these clinical studies were generated in Vietnam. Specifically, two clinical studies included sites in Vietnam—namely a randomized, double-Blind, double dummy, comparative, multicenter study to assess the incidence of hemolysis, safety, and efficacy of TQ (SB-252263, WR238605) versus PQ in the treatment of subjects with *Plasmodium vivax* malaria. The trial was conducted at seven hospitals or clinics in Peru, Brazil, Colombia, Vietnam, and Thailand, including investigational sites in Ho Chi Minh City and Hanoi. Further, a second study looking specifically at pediatric applications, an open label, non-comparative, multicenter study to assess the pharmacokinetics, safety and efficacy of TQ in the treatment of pediatric subjects with *Plasmodium vivax* malaria was also conducted in Vietnam.

Meta-analysis of these studies showed that efficacy of a single dose TQ (300 mg) together with CQ was not non-inferior to the efficacy to 14 days of PQ together with CQ for radical cure of *P. vivax* infection at 6 months. In those studies, TQ and PQ had broadly similar safety profiles.

There is clear potential to improve access to and utilization of RC using TQ + CQ. PQ requires a 14-day dose compared to a single day dose for TQ and a single day dose is likely to improve patient adherence to the treatment. However, a significant safety concern with both TQ and PQ is the high risk of acute hemolytic anemia (AHA) in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency or low levels of G6PD enzyme activity. G6PD deficiency is a common hereditary cell disorder affecting red blood cells in particular, with an overall prevalence across malaria-endemic countries of 8.0% (interquartile range, 7.4–8.8), corresponding to approximately 350 million affected individuals (Gething et al., 2012). Because of the risks associated with 8-AQ use among those with G6PD deficiency, the WHO recommends that “the G6PD status of patients should be used to guide administration of PQ for preventing relapse” (World Health Organization (WHO), 2021). The drug labels for both PQ and TQ have a caution for G6PD deficiency, and the TQ label more specifically recommends not prescribing TQ to patients with less than 70% G6PD enzyme activity.

The risk of hemolysis is dependent on the dose of 8-AQ, as well as on the degree of G6PD deficiency and the G6PD variant. Diagnostics tests that can identify those with G6PD deficiency and classify patients according to current case definitions are thus required. Quantitative or semi-quantitative tests allow identification of individuals with G6PD deficiency (<30% activity) and intermediate G6PD activity (approximately between 30 and 70% activity). G6PD deficiency is an

X-linked genetic disorder, thus males can either carry a G6PD allele that confers G6PD deficiency with activity levels typically below 30% or G6PD normal with G6PD activity levels typically above 60-70% (Anderle et al., 2018; Chu et al., 2020). Due to lyonization, heterozygous females express G6PD deficiency activity levels across a distribution with a mean typically falling within intermediate levels (30-70%) (Anderle et al., 2018; Chu et al., 2020).

The G6PD classification guides RC: G6PD deficient individuals are ineligible for the standard dose of PQ and individuals with less than 70% G6PD enzyme activity are ineligible for TQ. G6PD deficient patients can be treated with an alternative PQ regimen (i.e. 0.75 mg/kg bw once a week for 8 weeks). Thus PQ and TQ may be used within the same treatment algorithm and provided to individuals that meet the specific eligibility criteria, including G6PD normal or intermediate classification for PQ, and G6PD enzyme activity above 70% of the population median for TQ.

Given the remote settings where malaria is most prevalent, appropriate access to RC can only be achieved with the availability of tests for G6PD deficiency that can be used at the POC. POC diagnostics for G6PD deficiency are now available and have the potential to expand access to properly tolerated RC as well as enable significant progress towards malaria control and elimination goals.

One of these tests, the SD Biosensor STANDARD™ G6PD test is a POC test that has been evaluated in multiple countries including, Vietnam, Laos, Bangladesh, Brazil, Thailand, United Kingdom, United States, Bangladesh and Ethiopia (Alam et al., 2018; Anderle et al., 2018; Gerth-Guyette et al., 2021; Zobrist et al., 2021). The useability and ability of the test to distinguish between normal and intermediate or deficient individuals is good, with reported sensitivity and specificity ranging from 100-89% and 99-98% respectively in multiple evaluations (Zobrist et al., 2021).The SD Biosensor STANDARD™ G6PD test offers some benefits compared to qualitative tests: it can be used across a greater range of temperatures and humidity levels, it allows for the identification of patients with intermediate levels of G6PD deficiency (i.e. female patients) and it includes quality control reagents that can be used to train and certify users as well as to assess and maintain the quality of the test over time. The test has been registered in multiple malaria endemic countries, including Vietnam and received approvals from the Australian TGA. A WHO pre-qualification process is underway. This test has been adopted as part of routine care in Vietnam as well as Thailand, Cambodia and Lao PDR. It was evaluated in an operational research study in Vietnam in 2020-2021 where the study demonstrated that G6PD testing could be integrated into malaria case management at health facilities. It has since been scaled across malaria endemic facilities in Vietnam with support of the national malaria control program, PATH, and Health Poverty Action.

5.2 Background on the malaria burden and current case management in Vietnam

The number of malaria cases in Vietnam has come to a record low during the last 5 years. Annual confirmed cases stagnated around 4,000 cases in recent years, declined by a half in 2020, and continued to decline in 2021 with 467 cases (with 253 *P. vivax* cases accounted for 54.2% of all malaria cases), potentially as result of COVID-19's impact on population movement. However, as the overall burden of malaria continues to fall, the proportion of cases attributed to the more difficult to treat *Plasmodium* species, *P. vivax*, persists: In 2022 with the travel restrictions lifted, the total malaria cases were 456, similar to previous year, with 169 *P. vivax* cases. Additionally, outbreaks of *P. vivax* have been identified in several geographically remote areas across the country that previously reported very few, if any, cases. (NMCP, 2021). In last 2 years, the total number of domestic malaria cases has been gradually declining, in 2023 the total cases were 331 with 207 *P.vivax* and in 2024 the total cases were 270 with 70 *P.vivax*.

In approaching elimination, the country's epidemiological maps highlight distinct pockets where high caseloads are found in small populations, often in hard-to-reach and remote areas. Consequently, assurance of treatment adherence becomes much more challenging, especially with the long-course drug regimen required for PQ. The country's goal is to eliminate malaria by 2030. To do so, the Ministry of Health (MoH) is prioritizing several strategies to strengthen case management such as the use of active case detection, supplying G6PD diagnostic tools to health facilities, and updating of national technical guidelines (Health, National Plan for Malaria Control and Elimination , 2021-2025).

Further, there have been numerous studies of G6PD deficiency in Vietnam involving multiple ethnic groups, multiple provinces, and multiple G6PD test types. Modeling based on surveys done by the Malaria Atlas Project predict a G6PD deficiency prevalence of 8.9%. (Howes RE, 2012)

5.3 Diagnosis

In Vietnam, multispecies rapid diagnostic kits (RDTs) are recommended to be used at the health post level (e.g. lower level of the commune health station) while microscopy is recommended at the commune health station and hospital levels. Microscopy is sometimes used as part of active case detection or in situations where low parasite density infections may be expected.

5.4 Current case management strategies and practices

According to the latest national surveillance guideline (Health, National Guidance on Malaria Surveliance and Prevention 4922/QD-BYT, 2021), administrative areas (province, district and commune) are classified into 3 different phases of the malaria transmission continuum: control, elimination and prevention of re-establishment (PoR). This classification depends on the annual parasite index (API) at the commune level. A commune with a 5-year average API of ≥1/1000 at-risk population or at least one year with API ≥1/1000 at-risk population during such a period is in the control phase. If in the last 5 years, the commune has an average and all year-specific APIs of less than 1/1000, it is classified as part of the elimination phase. An 'elimination' district or province must have all its communes in the elimination phase. Finally, the PoR phase applies to districts and provinces which have been certified for malaria elimination by the MoH and are deploying a mix of interventions to prevent malaria from re-entering.

Passive case detection (PCD) is the conventional detection method where people present at primary health care centers for diagnosis and treatment. Active case detection can be further classified as 're-active case detection' (rACD) – which is triggered by an index case, and so-called 'proactive case detection' (pACD) – where a designated investigation team actively goes to a high-risk community or population for mass screening without the need of an index case.

Case detection practices are strategized locally according to the phases. Areas in the control phase are not required to carry out focus investigation. However, in the hotspot areas such as those of high endemicity, complicated epidemiological trend, prolonged transmission, increase in case load or at a high risk of outbreak, ACD can be implemented following the MoH guidance.

Areas in the elimination phase will carry out focus investigation if an initial investigation of a single case shows that local transmission is likely to happen. The area (i.e., village) will be classified as an active focus and rACD will be conducted as part of the response. Continuous ACDs are repeated weekly afterwards, then more occasionally (i.e., monthly in high season and lower frequency in low season). Targets of the rACD and its reaction chain are village residents and those at high risk such as forest- and plantation goers and cross-border travelers. The geographical scope, number of people to be tested and the time span for periodical testing are not specified and depend on specific circumstances. Foci will be re-classified on an annual basis. Those without a (suspected) local transmission within 1-3 years turn into residual foci and non-active foci after 3 years. In these latter types of foci, case detection should be intensified to some extent although it is not clear if ACDs are to be conducted.

Areas in the PoR phases are required to maintain routine case detection to suspected cases and people coming from at-risk areas. Whether PCD, ACD or both practices are to be applied is also not required in the national guidance and may depend on local availability of resources.

Under funding from the Regional Artemisinin-resistance Initiative (RAI) and other activities/projects from WHO and several other organizations, the NIMPE and local health authorities also carry out rACD and pACD in some high burden areas which are a subset of communes in the control phase.

The intervention model of the study will be designed with respect to the current case management practices in order to ensure compliance with national guidelines (e.g., of malaria surveillance, malaria diagnosis and treatment, pharmacovigilance), maximum of acceptability, minimum disruption to the health facility and workers' day-to-day responsibilities as well as optimum use of resources among all things considered. Current case management practices differ primarily as a result of different methods of case detection.

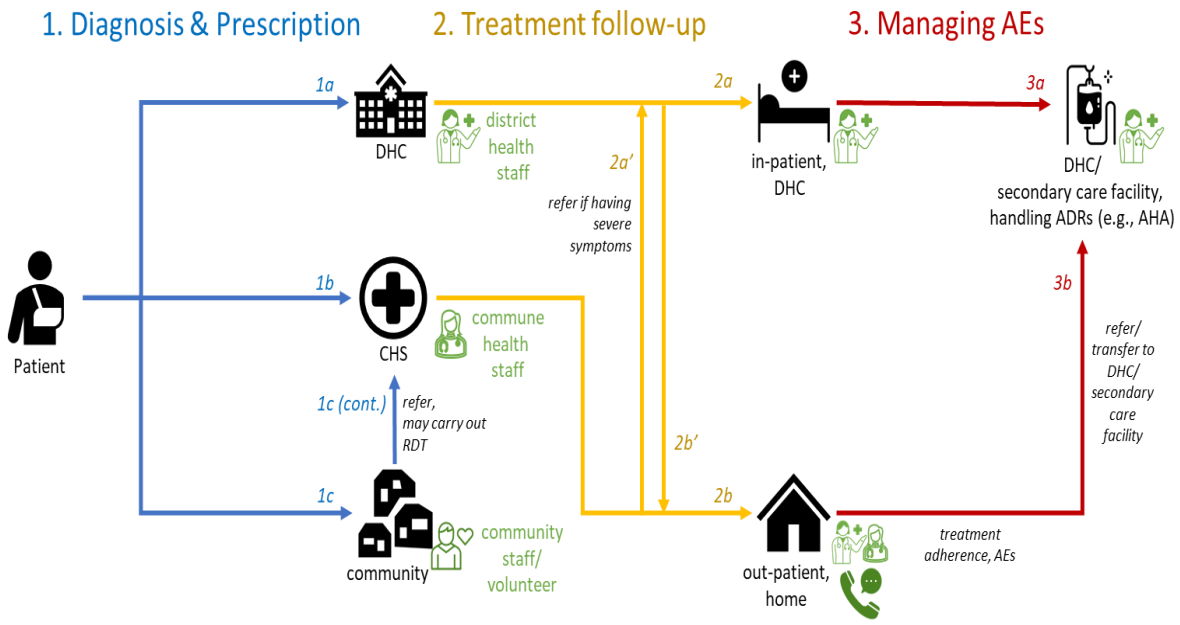
Passive case detection, see Figure 1– In this scenario, when feeling unwell, patients may go directly to a health facility at their convenience (flow 1a or 1b in the figure). Another possibility is that the patient is visited by health staff or volunteers at community level (flow 1c). The community level includes village health workers, community malaria action teams (CMAT) and malaria posts. While village health workers are part of a more permanent community health workforce in charge of different health areas and exist across the country, the latter two entities are specific for malaria, mainly funded by the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) and, therefore work only in Regional Artemisinin Initiative 3 Elimination (RAI3E)-covered high-burden areas. The community workforce may carry out diagnosis with malaria RDTs but is mostly in charge of referring suspected cases to commune health stations for confirmatory testing and treatment.

Once in the health facility, if the patient is confirmed positive with *P. vivax* malaria, they will receive clinical counseling and a drug prescription according to the current treatment guidelines. Depending on the severity, patients may be retained at the district health center (DHC) - in case they visit the DHC directly (flow 2a) or transferred from the commune health station (CHS) to DHC if they are diagnosed with severe malaria, show symptoms of complications, or as required by a specific study they participate in (flow 2a'). For the remaining cases, the patient is sent home for self-care (flows 2b and 2b'). During COVID-19 outbreaks, out-patient management practice is further encouraged in case of high emergency to prevent over burden to the facility and unnecessary hospital-acquired infection.

Retained patients receive care and direct follow-up from district health staff usually within 5-7 days of being released. In the meantime, those who are sent home are typically followed up by their counseling doctors or general practitioners via phone on Day 7 unless required differently in a pilot study or project.

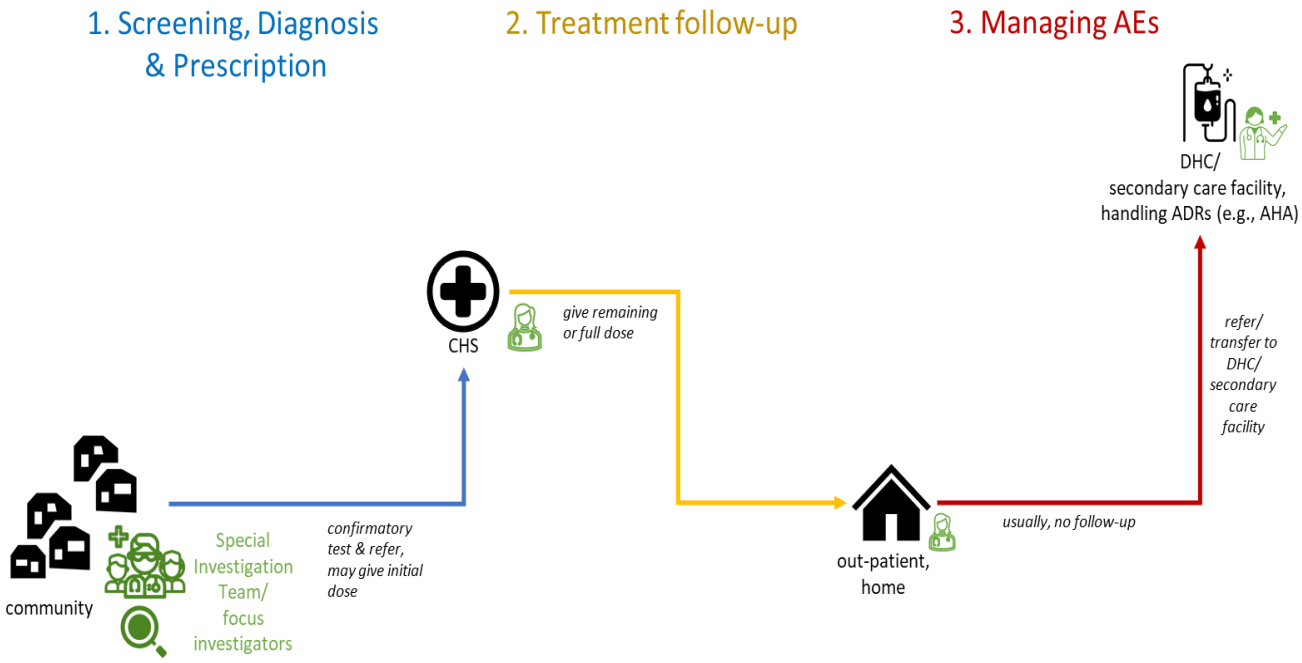
During treatment follow-up, if a severe or serious adverse event is detected, those who stay in the district health center will be treated immediately or transferred to a higher-level hospital (flow 3a), depending on the capacity and infrastructure of the district health center. In case a severe or serious adverse event is detected in an outpatient, the person will be referred or transferred by the doctor/general practitioner in charge or assigned person to the secondary health care center for handling (flow 3b). Monitoring and reporting of adverse drug reactions (ADRs) need to follow the national pharmacovigilance guidance. (Health, National Guideline on Pharmacovigilance , 2021) These guidelines indicate that clinicians are encouraged to report all adverse events to the national PV system but in practice, often only severe or serious AEs are reported, when clinicians are aware of them.

Figure 1: Current case management practice of *P. vivax* - PCD



Active case detection, see Figure 2 – Active case detection includes both proactive and reactive case detection. Reactive case detection is chiefly different from proactive case detection in the screening procedure. Reactive case detection is usually triggered by an index case in the community. Typically, a focus investigation team made up of district health staff, commune health staff and a village health worker will go to the community and take blood samples of residents and people at high-risk in a small area (i.e., a village) where the index case is identified. As for proactive case detection, a Special Investigation Team (including malaria staff from the provincial level and sometimes the central level) will reach out to communities at high risk of malaria to conduct mass screening. In both rACD and pACD, the outreach team will carry out confirmatory diagnosis at site and may or may not prescribe an initial dose for the patient then refer them to the commune health station to complete treatment (please refer to section 7.2.1). There, the patient will receive the remaining dose (if they already get the initial dose on Day 0 or Day 1) or the full dose. Most of the time, cases detected via active case detection methods are asymptomatic or uncomplicated. Thus, the patient is sent home for self-care. According to guidelines, the commune health staff in the catchment area is in charge of treatment follow-up for any malaria positive patients but systematic follow-up of these patients does not always happen in practice. Similar to passive case detection, if any adverse drug reactions are detected during the follow-up period, the commune health staff will refer the patient to a secondary care center and report the adverse event following PV guidance. The specific patient flow for each pACD and rACD campaign may change, based a number of factors including who is primarily running the campaign, the number of malaria positive individuals identified, and the specific context related to referral between community, commune and district facility levels. In some instances, G6PD testing and RC are provided at the community level as part of these campaigns and in others, patients are referred to complete treatment, including radical cure.

Figure 2: Current case management practice of *P. vivax* - ACD



Use of quantitative point-of-care G6PD testing and associated treatment – The national diagnosis and treatment guidelines recommend that health facilities carry out G6PD quantitative testing for *P. vivax* patient or G6PD qualitative testing in case the quantitative test is not available. (Health, National Guidance on Malaria Diagnosis, Treatment and Prevention, 2020) For male and female patients with G6PD activity less than 30%, they will receive 0.75 mg PQ base/kg/week x 8 weeks. For female patients with G6PD of 30%-70%, they will receive 0.25 mg PQ base/kg/day x 14 days. Since the recent WHO recommendation to provide the same total dose of PQ over 7 days, patients with normal G6PD activity may also receive 0.5 mg PQ for 7 days as well. This treatment option has subsequently been considered by the treatment guideline review committee and approved. Moreover, in the period 2021-2025, NIMPE is rolling out G6PD tests to health facilities down to commune level in strata 4 and 5 (the highest burdened areas) for use with all *P. vivax* and *P. ovale* patients following the national treatment guideline (Health, National Plan for Malaria Control and Elimination , 2021-2025).

In support for the country's decision to scale up the use of quantitative G6PD testing at points of care, PATH collaborated with the MoH to conduct an operational research study to assess its operational feasibility and the results were available by early 2022 (G6PD Operational Research in Vietnam, 2020). Health Poverty Action, a non-profit organization operating in Vietnam, is supporting this roll out and has obtained financial support to procure the STANDARD G6PD Test, provide capacity building and supportive supervision in nearly 30 health facilities at district and commune levels in the highest-burden areas. Thus, G6PD testing using the STANDARD G6PD Test is currently the standard of care for malaria case management both in policy and practice in high-burden areas. The treatment algorithm is based on the manufacturers recommended thresholds for determining G6PD status.

Patient follow-up as per national guidelines: National treatment guidelines entail that daily treatment follow-up of *P. falciparum* and *P. vivax* malaria patients is conducted to ensure sufficient doses to avoid malaria relapse. In routine practice, after taking drugs of the first day at heath facility, patients may return home, they are asked to come back to the health facility for follow-up regarding treatment administration and to conduct a microscopy evaluation of a blood smear to assess treatment failure. Compliance with this recommendation is highly variable and depends on how far patients live from the health facilities as well as whether they are recommended to stay at the health facility post-treatment. Compliance with these follow-up visits is expected to improve as part of a research study where aspects of the follow-up are incentivized on the part of both providers and patients.

Registration of TQ in Vietnam – At the time writing this study protocol, the manufacturer, GlaxoSmithKline has applied for registration of 150-mg tablet tafenoquine in Vietnam under the brand name Kozenis; and TQ was licensed for commercial use by related authorities in October 2024. The use of TQ will follow related in-country regulations (e.g., on triage system, pharmacovigilance, emergency treatment and intensive care). In addition, monitoring the frequency of new malaria infections in study participants after first encounter treatment will provide valuable information for NIMPE to anticipate the potential impact of using TQ in various case-finding strategies.

- As mentioned in the section 5.1 above, TQ had been clinically tested for safety in all 3 phases, and for efficacy in phase 2 and phase 3 for licensing purpose according to the FDA, EUA regulations. This drug has been registered in US, Australia, Brazil, Peru, Thailand, the Philippines and Colombia. The safety and efficacy data are summarized in the appendix of TQ package insert of the protocol. In addition, there were a sub-study of phase 3 clinical trial and another sub-study of phase 2 trial conducted in Vietnam whose data were included in the application package for registration. A Randomized, Double-Blind, Double Dummy, Comparative, Multicenter Study to Assess the Incidence of Hemolysis, Safety, and Efficacy of Tafenoquine (SB-252263, WR238605) Versus Primaquine in the Treatment of Subjects With Plasmodium Vivax Malaria. 300 patients were enrolled at seven hospitals or clinics in Peru, Brazil, Colombia, Vietnam, and Thailand
- An Open Label, Non-comparative, Multicenter Study to Assess the Pharmacokinetics, Safety and Efficacy of Tafenoquine in the Treatment of Pediatric Subjects With Plasmodium Vivax Malaria. This study enrolled 60 pediatric patients in Vietnam and Colombia

Information about the dosage, administration, contraindication and special warnings and caution for use of TQ are provided in the appendix of TQ package insert of the protocol.

5.5 Study rationale

Widespread adoption of these new tools, particularly the use of TQ, into national treatment policies and practices requires demonstration that they can be used effectively across different levels of healthcare systems. The appropriate and systematic use of the SD Biosensor G6PD test, the effective use of TQ, the identification of patients at risk of hemolysis prior to treatment, and the adequate follow-up of patients represent significant implementation challenges for malaria control programs, even more so at the community level where most vivax patients often seek care. A key element in the decision to adopt these tools is whether they can be successfully integrated into malaria case management algorithms by the providers within health systems. In addition, the costs of these tools as well as the overall cost of implementation is crucial.

The use of these tools together will require the revision of the current diagnostic and treatment guidelines; and the revised guidelines will include TQ after G6PD testing. The use of the point-of-care test for G6PD to inform treatment decisions with primaquine has already been demonstrated in multiple countries including Vietnam. The use of the STANDARD G6PD test has also been shown to support treatment with tafenoquine in Brazil and is currently under evaluation in Thailand but only in the context of passive case detection. Studies that investigate the operational feasibility of using these tools combined, identify possible implementation challenges, and explore ways to address them are crucial for future adoption and scale-up. Malaria programs in multiple endemic countries are currently building evidence and gaining experience with the use of the STANDARD G6PD test followed by RC. There is a clear need to investigate further the feasibility of using this test with both PQ and TQ, as the eligibility criteria for each differ.

The country's goal is to eliminate malaria by 2030. To do so, the MoH is prioritizing several strategies to strengthen case management such as the use of active case detection, supplying G6PD diagnostic tools to health facilities, and updating of national technical guidelines. (Health, National Plan for Malaria Control and Elimination , 2021-2025) TQ was approved for radical cure of malaria by the US's Food and Drug Administration (FDA) and the Australian's Therapeutic Good Administration (TGA) as

well as for RC in Brazil, Peru, Colombia, the Philippines, Thailand and recently in Vietnam (October 2024). With known efficacy for targeting liver-stage hypnozoite and single-dose administration for RC, TQ is expected to accelerate the progress of malaria elimination.

The successful implementation and adoption of a new diagnostic and treatment algorithm will require implementation challenges to be anticipated, understood, and resolved at multiple levels of the health system. This study will propose a package of interventions that includes the revised algorithm as well as supportive interventions such as training and supervision and best practices for using G6PD testing with radical cure as part of ACD campaigns. In brief, the revised algorithm proposes to add G6PD deficiency testing and TQ administration as a treatment option to the current algorithm. The study then aims to assess primarily the operational feasibility of implementing RC with TQ and G6PD tests from the health system perspective to serve as an instrumental input to future roll out and scaleup considerations of the national malaria program.

6 Study goals and objectives

6.1 Study Goal

The goal of the study is to generate evidence to assess whether the use of TQ for RC of *P. vivax* malaria is operationally feasible in a country approaching elimination. Based on the evidence collected, this study will identify the capacity gaps and system bottlenecks that should be addressed for successful scale-up and sustainable use of the drug as well as adaptation/improvement strategies to ensure best fitting of the intervention model with local context and various local sub-settings (e.g., national case management guidance, degree of transmission, case detection strategies being used). All these findings and recommendations can, in turn, be used to inform the country's malaria treatment policy and facilitate cross-country learning.

6.2 Study Objectives

The study aims to achieve the following specific objectives:

Primary objective:

Assess adherence to a new case management algorithm for *P. vivax* malaria (that involves providing RC after semi-quantitative G6PD testing and follow-up visits) in varying case management strategies. This will be assessed from the patient perspective.

Secondary objectives:

1. Determine the capacity of the health system to safely implement RC after G6PD testing in different case finding strategies.
2. Assess the quality and effectiveness of training and supervision strategies through competency testing, and training and supervision evaluations.
3. Explore barriers and facilitators to adding TQ to the treatment algorithm at national level within different case finding strategies.
4. Determine the costs associated with introducing a single dose RC.
5. Monitor the frequency of recurrences in study participants after treatment up to day 29
6. Monitor SAEs in study *P.vivax* patients receiving RC

Exploratory objectives:

1. Monitor moderate and severe adverse events in study *P.vivax* patients receiving RC

7 Study design and methods

Operational feasibility of the implementation package (detailed below) will be measured across multiple dimensions: whether patient treatment decisions align with the revised algorithm and patient G6PD status, patient follow-up and safety, modified training and supervision strategies, patient and provider perceptions, and costs. These dimensions will be investigated through an approach that will include a quantitative component that assesses adherence to case management guidelines at the patient level, a qualitative component, and a cost analysis component. The data and information generated through these different components will collectively help assess the operational feasibility of providing RC (TQ and PQ) after G6PD testing.

This study will use mixed methods, including the quantitative assessments of case management data, qualitative assessments (including interviews, focus group discussions), and a costing component that compares costs across case-finding strategies. Intervention safety will be measured through a follow-up visit of patients to identify, manage, and assess any instances of AHA. New infections will be monitored through patient follow-up as well as through national surveillance data.

Research participants will include vivax patients and their caregivers, health care providers involved in the delivery of malaria case management, and health administrators involved in the supervision of malaria case management. The study will be implemented in 12-36 selected commune health stations in 7 districts of 6 provinces which are Lai Chau, Gia Lai, Binh Phuoc, Phu Yen, Khanh Hoa and Quang Tri as well as through active case detection activities conducted by NIMPE. Additional sites may be added to reflect where cases are occurring based on epidemiologic data.

This study is a longitudinal, uncontrolled, low-interventional study, that uses a mix of methods to evaluate the operational feasibility of introducing new tools in the management of vivax patients. This study includes a revised case management algorithm and other adaptations to routine malaria service delivery required for successful implementation of new tools. It does not evaluate the primary efficacy or safety of the component diagnostic or drug treatments, both of which have been previously evaluated. (Lacerda et al., 2019; Llanos-Cuentas et al., 2014; Zobrist et al., 2021)

7.1 Conceptual framework

The logic model used to guide the design of the study is shown below. This model starts with a statement of the initial gap to be addressed by the study: the fact that vivax patients may lack access to best clinical practices for diagnosis and treatment. The second component is the evidence-based intervention that is to be implemented and disseminated. The implementation strategies correspond to methods used to enhance adoption, implementation, and sustainability of the intervention. These include the revised treatment algorithm, a multi-faceted training program, strengthening of patients' follow-up and monitoring of AHA, as well as other strengthening of existing systems and processes (e.g. PV and integration into ACD). Finally proximal and distal outputs and outcomes are listed.

Table 3: Adapted logic model used to guide study design, conduct and reporting, based on the NIH for Dissemination and Implementation (D&I) Science projects (Smith et al., 2020).

	Inputs		**Proximal outcomes**	**Distal outcomes**	
Problem/Gap	New tools	Implementation strategies	Outputs	Intervention impact	Long-term outcomes

P. vivax patients do not consistently have access to best clinical practices due to lack of options for G6PD testing and limited coverage of RC. Patient may not be cured due to poor adherence to a 14-day treatment regimen Elimination efforts may be undermined by on-going transmission of vivax malaria due to lack of eradication of liver stage parasite	G6PD test, and single dose RC	• Integration of new tools into revised case management algorithm including active case detection strategy. • Training of health care providers • Strengthening of patient's follow-up and monitoring of AHA. • Supportive supervision mechanism • Local adaptation	• Revised case management algorithm that includes new tools and active case detection strategy. • Training curriculum • Working instruction and job aids. • Patient counselling material • Lesson learned for systems and service delivery strengthening	• Patients receive appropriate care in line with best practice. • Increased number of patients are treated and cured with an effective RC.	• Lower vivax recurrence rates resulting in decreased transmission and burden.

7.2 Target implementation package

This study aims to introduce a revised case management algorithm and other adaptations to routine malaria service delivery required for the successful implementation of new tools. This intervention will include the following components:

- A revised *P. vivax* treatment algorithm that incorporates new radical cure tools (G6PD test + TQ) and deployment strategies as part of passive and active case detection
- The training of health care providers and malaria program staff in the revised algorithm and the use of the new RC algorithm
- Patient counselling
- Strengthening follow-up visits
- A quality monitoring of *P. vivax* case management

This intervention will be implemented at the commune health station level, serving as a demonstration of the revised case management algorithm in selected health facilities.

7.2.1 Standard of Care and current service delivery model

The 2021 WHO guidelines for malaria indicate that *P. vivax* infections can be diagnosed either by microscopy or using RDTs based on immunochromatographic methods (World Health Organization (WHO, 2022). To prevent relapses, the blood-stage treatment should be followed by a course of PQ. The guidelines further state that the G6PD status of patients should be used to guide administration of PQ for preventing relapse. Total doses of 3.5 mg base/kg bw (0.25 mg/kg bw per day) are required for temperate strains and 7 mg base/kg bw (0.5 mg/kg bw per day) is needed for the tropical, frequent-relapsing *P. vivax* prevalent in East Asia and Oceania. These dosing recommendations apply to G6PD normal patients. For mild-to-moderate G6PD deficient patients, a 0.75 mg/kg bw dose given once weekly for 8 weeks is recommended. PQ is contraindicated in pregnancy and lactation <6 months post-partum unless the infant has been tested for G6PD deficiency.

The Vietnam National Malaria Guideline recommended diagnosis and first line antimalarial drugs for *P. vivax* are the following:

- At hospital and health center levels clinicians should diagnose malaria based on the microscopic examination of patient blood smears. At the health post level, Village Health Workers (VHWs) should make a diagnosis of malaria using a multi-species RDT. In ACD campaigns, both RDTs and microscopy are used.

- To prevent relapse of *P. vivax* malaria, children, and adults (except pregnant women, infants less than 6 months of age, women breast feeding infants less than 6 months, women breast feeding older infants known not to be G6PD deficient and people with G6PD deficiency) are treated with a 14-day course of PQ in all transmission settings at all levels of the health system. Pregnancy and breast feeding status are assessed by asking the female patient. Health workers should be vigilant to detect side effects of PQ.
- The first line drug of choice is CQ plus PQ RC. CQ preparation is 150 mg base tablet. PQ is given at a dose of 0.25mg/kg per day for 14 days. National guidelines were updated to include the recently recommended 0.5mg/kg per day for 7-day regimen for normal G6PD patients in addition to the existing 14-day regimen if G6PD testing is not available.
- Mixed infection confirmed by microscopy are treated with Pyramax® (pyronaridine-artesunate) and 7 days course for normal G6PD patients of PQ or 14 day course if G6PD testing is not available.

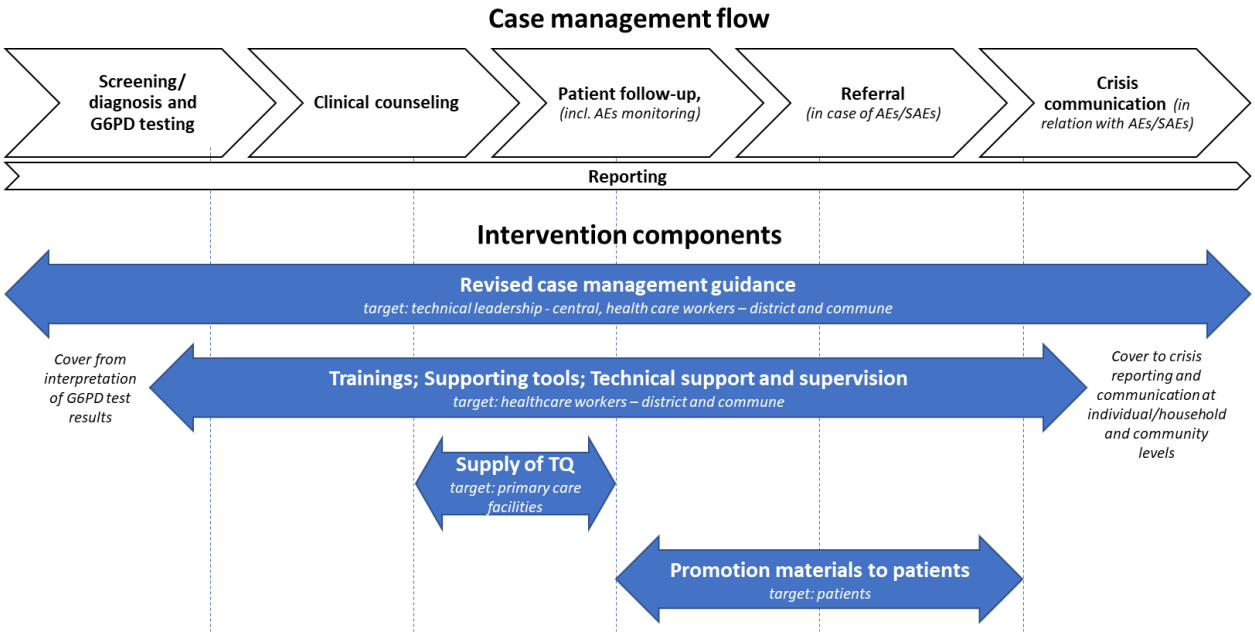
In Vietnam, within these treatment guidelines, the specifics of how patients are diagnosed and treated may also depend on the region of the country and the level of the health system at which they are seeking care.

There are multiple steps involved in malaria case management, and depending on the size of the facility, they may be conducted by multiple HCPs. Community health workers, or Village Health Workers (VHWs) are responsible for the provision of malaria case management services at health posts, the lowest levels of care.

7.2.2 Implementation package

Considering the above aspects of the local context, the existing health system, and current case management practice, the core intervention package is designed to ensure maximum integration with existing practices and while capturing the full range of feasibility questions. Elements of the core package are described below and how the elements are integrated into a typical case management flow are elaborated in Figure 3.

Figure 3: Components of the core intervention package and their breadth of coverage in relation to a typical case management flow (i.e., all potential encounters of one patient with service providers) of *P. vivax* using TQ for RC



7.2.2.1 Revised case management algorithm

A revised case management algorithm is the most fundamental part of the intervention package (Figure 5). It will serve as a basis for the content of the other activities and cover different processes throughout the continuum of services, from interpreting G6PD diagnosis results, prescribing TQ, requirements for treatment follow-up, monitoring adverse events, and reporting adverse drug reactions. Based on the existing national diagnosis and treatment guideline and case management practice, additional and adjusted criteria are to be provided to high-level supervisors, and district and commune health staff at the study areas.

Interpretation of G6PD diagnostic results –

- In the current national diagnosis and treatment guideline, a G6PD quantitative or qualitative diagnosis is recommended rather than compulsory for *P. vivax* patients. For potential subjects of this study, the STANDARD G6PD Test (SD Biosensor) a POC G6PD semi-quantitative test will be conducted. Currently, no qualitative G6PD tests are used as part of malaria case management.
- The thresholds for G6PD normal status for use in primary care facilities are those recommended in the instruction for use of the SD Biosensor's STANDARD G6PD Test as specified in Figure 4. To minimize the risk of RC-induced hemolysis amongst patients with G6PD deficiency, confirmed *P. vivax* patients with G6PD enzyme activity level of less than 70% of the value for G6PD 'normal' activity will not be eligible for TQ regardless of sex. This is in line with the TQ product intended use.

Figure 4: Threshold recommendations of G6PD level status per instruction for use of the STANDARD G6PD Test

INTERPRETATION OF TEST RESULT

Male		Female	
G6PD Deficient*	≤ 4.0 IU/g Hb	G6PD Deficient*	≤ 4.0 IU/g Hb
G6PD Normal	≥ 4.1 IU/g Hb	G6PD Intermediate**	4.1-6.0 IU/g Hb
		G6PD Normal	≥ 6.1 IU/g Hb

*Deficient was determined during clinical evaluation as approximately 30% of the adjusted male median of specimens tested.
**Intermediate was determined during clinical evaluation as females with activity greater than 30% and less than or equal to 70% of the adjusted male median.

- To ensure safety of the treatment under study, the pilot health facilities must have functional G6PD tests and the capacity to perform such test.

Prescription of CQ-

- The CQ dosage will follow the current national guideline as extracted below.
- Dosage is determined by weight if a scale is available. The total dose of 25 mg base/kg is divided into 2 intakes, 6 hours apart on the first two days and one intake on the third day as follows:
    - Day 1: CQ phosphate 10 mg base/kg body weight.
    - Day 2: CQ phosphate 10 mg base/kg body weight.
    - Day 3: CQ phosphate 5 mg base/kg body weight.
    - If no scale is available, CQ dosing is determined by age group:

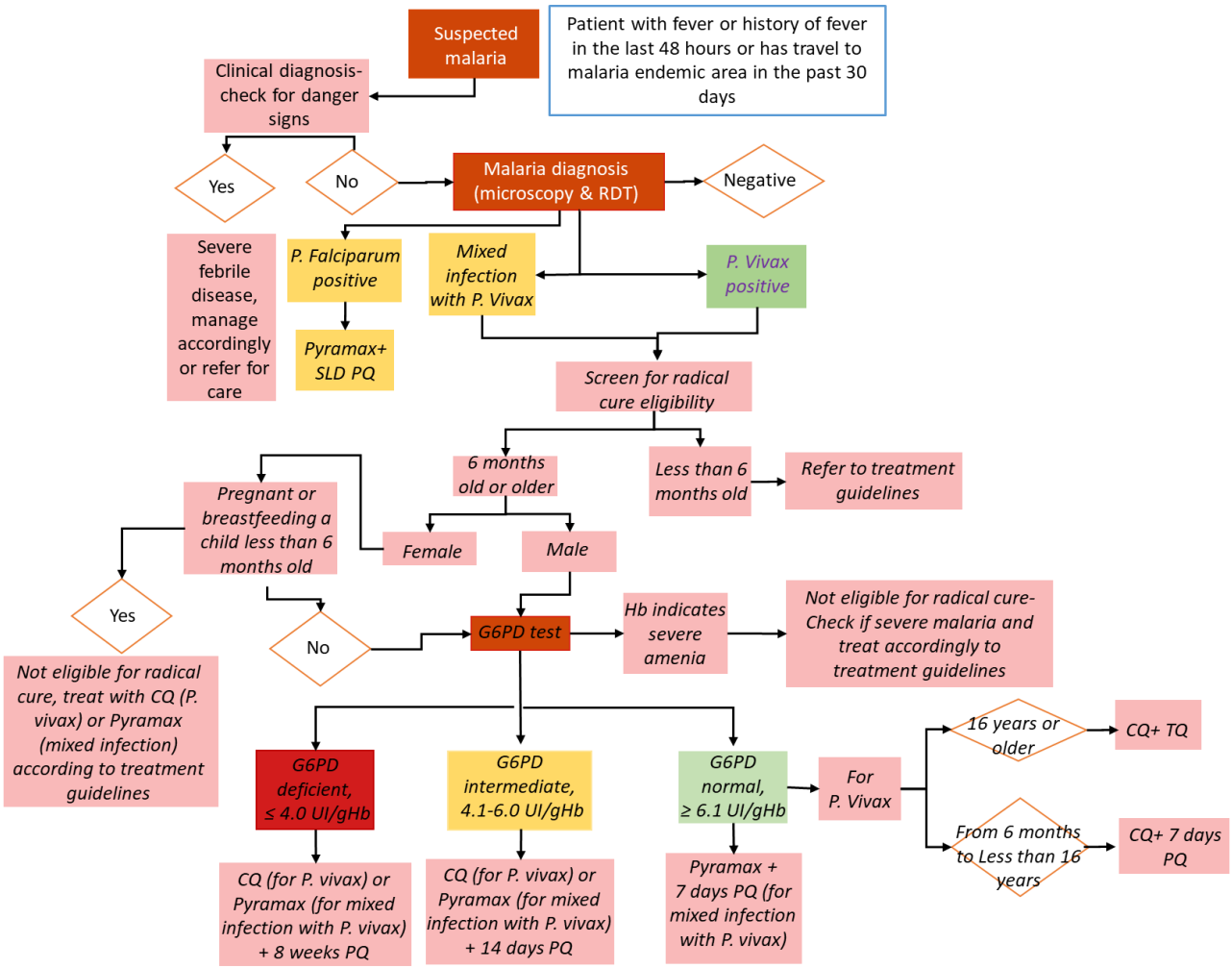
Age group	**Day 1 (tab)**	**Day 2 (tab)**	**Day 3 (tab)**
Under 1 year	½	½	¼
1 – under 5 years	1	1	½

5 – under 12 years	2	2	1
12 – under 15 years	3	3	1 ½
15 years and above	4	4	2

Prescription of PQ or TQ –

- At the time of writing this document, the manufacturer, GlaxoSmithKline is registering for marketing of TQ in Vietnam under the brand name Kozenis® and in the form of tafenoquine 150mg-tablets. Therefore, hereby this study will refer to the product information of *Kozenis* approved by the Australian TGA as the latest official information of the productTQwas approved for use in Vietnam in October 2024, prescription will follow the information approved by the Vietnam Ministry of Health and relevant authorities.
- Subjects who are enrolled and meet all TQ eligibility criteria will receive a single dose of TQ 300 mg (2 tablets of *Kozenis* 150 mg) on Day 1. Other indications and contraindications of TQ prescription will strictly follow the approved product information. Patients who do not meet all TQ eligibility criteria will receive the standard dose of PQ, as per national guidelines, based on other eligibility criteria including G6PD status.
- As TQ is prescribed, the other 8-aminoquinoline, PQ, will not be given to the study subjects.

Figure 5: Revised treatment algorithm



*The national treatment guidelines was revised in August 2023 to include 7 day PQ and single dose TQ for G6PD normal patients.

Treatment follow-up monitoring and reporting of adverse events –

- During clinical consultation at the health facility on Day 1, the health care worker will also give advice to patients to immediately seek medical attention if there are any signs of AHA. These signs include dark (Coca Cola colored) urine, yellowing of skin and/or sclera (jaundice) pallor, back pain, breathlessness or shortness of breath (tachypnea), rapid heart rate (tachycardia), fever, fatigue, dizziness, nausea and/or vomiting and will be included in all study training materials.
- When prescribing RC, the counseling doctor or general practitioner will ensure that the patients are aware of the potential risks associated with taking the drug. This information is also included as part of the informed consent process.
- Follow-up for treatment adherence, safety, and treatment failure from the health care worker will be conducted according to the current treatment guidelines and supplemented for additional study-specific requirements. The follow-up on Day 2,3, 4 and 8 will be conducted in person and the follow-up on Day 15 and 29 will be conducted remotely via phone call or home visit. At these follow-up encounters, suspected AHA will be identified using a specific protocol and suspected AHA will be further referred and investigated by the study team using a dedicated form and protocol for suspected AHA. The processes for addressing AHA and reporting to the appropriate PV authorities are outlined below. These follow-up visits will be reimbursed for both patients and health care providers in line with standard reimbursements for participation in a research study, which are outlined in the respective consent forms for all study participants.
- In the event of AHA or SAE, the health care worker in charge or an assigned community health worker/volunteer will immediately transfer the patient to the nearest secondary care level for necessary testing and handling of the adverse event, including but not limited to blood transfusion.
- The handling and reporting of events will comply with the national guidelines on pharmacy, pharmacovigilance, and other related official guidance. The study will monitor all moderate, severe, and serious adverse events and report to the PV system, the ethics review boards of record, and report AHAs and SAEs to the Sponsor.
- In the event of long-term, permanent impairment or serious adverse drug reactions, besides following the national guidance and compulsory protocols, the health facility and/or health care worker will comply with a preset communication plan to deliver the facts and appropriate messages to the relevant stakeholders at individual, household, and community levels such as the patient, the family of the patient and the head of the community.

7.2.2.2 Additional elements of the implementation package

The use of the algorithm will be supported by the following elements of the implementation package:

a) Training of HCP in the revised algorithm and the use of the new RC tools
   - At the beginning of the study, training courses will be provided to high-level supervisors (i.e., NIMPE staff, researchers, independent clinical monitoring officers) and eligible health staff (i.e., doctors/physicians and malaria focal points) of the selected health facilities. The training curriculum will include the revised case management algorithm, requirements for study participants (e.g., reporting, ethical concerns, confidentiality), contraindication of radical cure especially pregnancy and breastfeeding status, and use of the supporting tools and additional report forms.
   - Pre- and post-training assessment of knowledge, attitude and practice of the revised case management algorithm will be carried out to all targeted learners. Only those who pass the post-training assessment and agree to participate in writing will join the study. The threshold for passing the assessment is anticipated to be a score of 80% or higher. This training

assessment will include specifics regarding the revised algorithm and key contraindications for radical cure.
- The training curriculum will be validated by NIMPE leadership before dissemination.

b) Patient counselling
- A specific process will be put in place for patient counselling and standard tools including a counselling checklist will be developed to assist HCPs.
- To minimize risks to the participating patients, at the time of clinical counseling, they will be given a leaflet containing important information for the patients such as signs of potential adverse events, contact number of the counseling doctor/general practitioner, contact and address of the secondary health care center. Additional information that may be necessary for the health care center in handling emergency situation such as the patient's blood type from clinical record if available, a statement that the patient was given the long plasma elimination half-life 8-AQ as well as the dosing, and date of TQ intake will also be included in the leaflet.

c) Supportive supervision of the revised algorithm implementation
- NIMPE staff and in-country investigators will provide two (one primary, one alternative) in-use phone numbers and email addresses to the participating health staff for technical support throughout the implementation of the study.
- NIMPE staff and in-country investigators will also organize supportive supervision visits to pre-selected health facilities under the study for on-site support, refresher training as needed, quality control, data collection and other purposes depending on actual situations. Given that the revised case management algorithm will be new to health care providers early in the study, such central-level supportive supervisions will be provided more frequently for the first three months since the study start and on a quarterly basis afterwards.
- The study team of NIMPE and PATH will also conduct mid-term and end-of-term supervision visits to evaluate the overall implementation and collect qualitative data.
- District malaria focal points will pay a monthly visit to commune health stations under the study for on-site support, data collection as required, and report any issue found to NIMPE and/or the investigators.

7.2.3 Supplementary contents in the event of active case detection campaigns

The current practice of active case detection is different from that of passive case detection, mainly in the shared responsibility for screening and diagnosis between the investigation team and the commune health care worker. This study will include additional emphasis in training on the revised case management algorithm in the event of ACD. The aim of such supplementation is to:

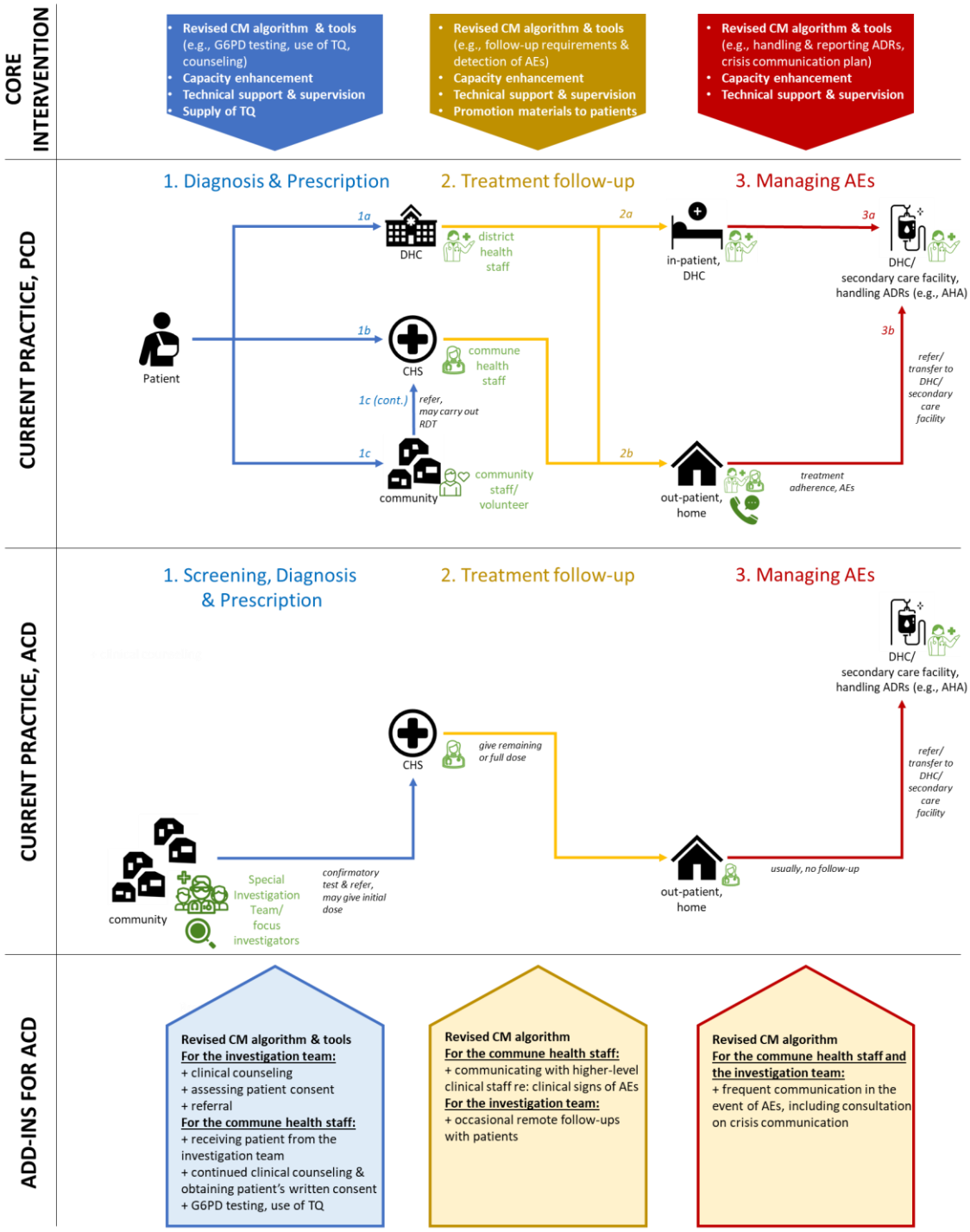
- Have defined roles and responsibilities for the field investigators and commune health workers in their joint task of screening, diagnosis and prescription.
- Facilitate proper communication between the field investigators and commune health workers throughout the case management flow; and
- Leverage high-level support and quality control from the investigation team.
- Ensure patient safety in the context of using a single-dose radical cure.

As described above, each ACD campaign includes a patient flow that aligns with the context of the campaign in terms of whether patients are referred to the commune or district hospital for G6PD testing and RC. For the revised treatment algorithm, the specific patient flow will be designed in collaboration with NIMPE and the Special Investigation Team prior to the campaign. In each campaign, the study team will ensure that: *P. vivax* diagnosis is confirmed; G6PD testing takes places prior to radical cure administration, and that the timing of both CQ treatment and RC is maintained according to the requirement for each drug.

Based on the specific context of each ACD campaign, patients may be testing for malaria in the community and then referred to a facility for G6PD testing and RC. They may also be screened for

G6PD status in the community, begin RC, and then referred to the facility for follow-up. similar to cases detected passively, health staff will follow up with the patients via phone or in person on Day 4 and Day 15 Here, the commune health worker may be recommended to consult with the higher-level clinical staff in the field investigation team when they suspect any symptoms of AHA or have any concerns during the follow-up with patients. The higher-level clinical staff in the field investigation team should provide expertise when being consulted by the commune staff and occasionally follow up with some patients directly via phone to ensure the service quality provided by the commune level. In the case of suspected AHA or a serious adverse event or severe adverse event, the commune health staff will be recommended to have frequent communication with the Special Investigation Team to determine how the event should be handled. For moderate adverse events, the commune health staff can handle them and will communicate with NIMPE investigator to record them in the AE report form. Figure 6 illustrates how the core and supplementary intervention elements are incorporated into current case management practices.

Figure 6: Components of the core intervention package and how they are used to strengthen the current case management practice (i.e., all potential encounters of one *P. vivax* participating patient with service providers)



7.3 Adherence to case management algorithm

The primary objective of the study is to assess adherence to a revised case management algorithm for *P. vivax* malaria that involves providing RC after G6PD testing and follow-up visits. This objective will be assessed at the patient level.

This component of the study will assess several endpoints that reflect adherence to the revised treatment algorithm and patient follow-up. Those endpoints will be computed based on individual patient data that will identify an individual as being correctly treated or not based on the revised

algorithm. When the prescribed treatment is not aligned with the revised case management algorithm, patients will be categorized as incorrectly treated.

7.4 Health care provider capacity and training evaluation

The quality and efficiency of training is to be evaluated as part of the study secondary objectives. This will be investigated through several dimensions, one of them being through a standardized competency assessment of each HCP. This competency assessment will include knowledge and understanding of thematic areas included in the training package, such as:

- *P. vivax* malaria and G6PD deficiency
- procedure for performing the SD Biosensor test for G6PD
- interpretation of the G6PD test results
- treatment with 8-AQ
- patient counselling
- identification and reporting of AHAs and SAEs

The quality of training will be evaluated through an HCP satisfaction questionnaire and through qualitative assessments. HCP will be assessed and retrained as required during the course of the study.

7.5 Qualitative component

The overall objective of the qualitative assessments is to understand patient and provider acceptability of and experience with *P. vivax* new RC algorithm, namely the G6PD test and TQ, as well as all related supporting interventions. This component will aim to achieve the following:

- Understanding and characterizing the context at health facilities (HF) prior to intervention: this will be done through a process of document review, key stakeholder interviews, and observation.
- Evaluation of the training and supervision strategy: this will be done through interviews with training and supervision participants. This will be conducted after the initial training and at one or more additional points during the study.
- Evaluation of the perceptions and acceptability of the RC algorithm and revised case management algorithms. This will be done with patients and providers through interviews and focus group discussions. This will be conducted after the initial training and at one or more additional points during the study.
- Evaluation of access and operational challenges encountered during the study: this will complement the data gathered through routine monitoring. Through qualitative assessment & documentation, the study will assess any issues, as perceived by relevant health workers, that directly impact HF ability to use the revised algorithm. This will be conducted at one or more additional points during the study.
- Investigation of how to best integrate the new tools within the existing surveillance, pharmacovigilance (PV) and supervision systems: this will complement the data gathered through routine monitoring. Potential barriers and challenges will be explored. This will be conducted at one or more additional points during the study.
- Identification of areas of improvement: Suggestions for improvement will be gathered through interviews with participants that are directly or indirectly exposed to the new RC algorithm. This evaluation will be conducted at one or more additional points during the study.

7.6 Costing component

The costing component of the study aims to assess the costs associated with introducing and integrating point of care G6PD testing into routine *P. vivax* case management, at different levels of the health services. This includes the incremental costs to existing costs of routine practice associated with the use of a single-dose radical cure with different case detection strategies. Importantly, given that G6PD testing is already recommended as part of routine care in Vietnam, this component will aim to assess the incremental cost of the specific intervention, inclusive of additional costs for active case detection, training, and supervision, but will not include the costs associated with routine G6PD test use.

The cost description will be conducted from the perspective of the malaria program at the health facility level. A consensus-based process map will be developed to identify the cost drivers that will be incurred after adoption and implementation/scaling up of the intervention package. Major cost drivers have been identified to include the cost of commodities, specifically the G6PD analyzer and test devices, as well as the cost of training. This will be validated with the MoH, and cost estimations will be conducted thereafter. Costs incurred by the patient will not be collected as malaria diagnosis and treatment is provided free of charge to patients in Vietnam.

The main cost categories include, but are not limited to:

- Training of health care staff on G6PD testing and the revised treatment algorithm including additional refreshment training requirements. This includes training of trainers as well as training of facility and ACD staff. This cost will include the cost of organizing the implementing the training (in terms of per diems, logistical and facility costs). These costs will be both fixed and variable, based on the numbers of trainings required and the number of participants in each training.
- Commodities (G6PD supplies, including sufficient analyzers for each facility and to use as part of ACD campaigns and sufficient supplies to use as part of quality control and quality assurance testing, TQ single dose radical cure) Commodity costs will include the cost of importing supplies.
- G6PD testing quality control. As part of G6PD testing implementation, G6PD analyzers will be assessed using to ensure that the analyzers are working properly. These quality control activities will take place at regular intervals as well as when any issues with the analyzers arise. These costs will include the costs of the reagents and test strips used in the quality control testing.
- Management of AHA cases due to incorrect treatment. These costs will include any resources required to transfer patients to higher level facilities, as well as the estimated cost of treating the patient, including additional diagnostic testing and treatments such as blood transfusions. These costs will only be incurred in the case of suspected of confirmed AHA cases.

Changes in malaria case management processes, including time spent on the G6PD test will not be included. This is due to the fact that G6PD testing is already recommended and practiced as part of the national treatment guidelines and that no additional staff are needed to perform the test.

The aim of the cost description is to inform national and donor budgets. It will quantify potential incremental financial costs to the MoH should they choose to incorporate G6PD testing and the revised treatment algorithm into routine *P. vivax* case management and to include active case detection strategy in the elimination program. This will only focus on costs that would be incurred after a policy change decision has been made. Costs related specifically to the research are out of scope, and no patient costs will be collected. Cost data will be prospectively collected for all costs incurred for integrating the G6PD test into routine care at representative study sites. Cost will be collected from all involved facilities.

7.7 Measures to mitigate bias and confounding

Potential biases include selection bias and information bias. Selection bias can occur if the study population is not representative of the target population. To mitigate for selection bias, the study will

- Ensure that the rationale for HFs to be included in the study are objective and justifiable. Purposive sampling of health facilities will be used to select study sites according to specific criteria, to accommodate a range of levels of the health system, malaria burden and accessibility; and alignment with current national treatment guidelines and standards was also considered. Site selections were done carefully and shared with a range of stakeholders, including the MoH. Characteristics of these facilities will be taken into account during the analysis and this limitation will be acknowledged when reporting study results.
- Minimize the extent of missing data through regular monitoring, and ensuring completeness and accuracy of data collected
- Residual selection bias may occur in respect of the rates of patient follow-up. The study will cover transport costs for patients to attend follow-up visits. As such, rates of follow-up may be higher in the study compared to routine care. This limitation will be acknowledged when reporting study results.

Information bias will be controlled for by using objective outcomes measures. All key information to assess adherence to the revised algorithm will be recorded on standard forms, including patient's characteristics, lab test results and the treatment.

7.8 Summary objectives, corresponding endpoints, and methods for data collection

Table 4: Study objectives, corresponding endpoints and methods for data collection

Study objective	**Outcome measures**	**Study component**	**Data collection method**
Primary Objective: 1. Assess adherence to a revised case management algorithm for vivax malaria that involves providing TQ and PQ after semi-quantitative G6PD testing and a follow-up visit.	**Primary endpoint(s)**: • 1.1. Proportion of vivax and mixed infection patients that are correctly treated with TQ and PQ based on the revised algorithm • 1.2. Proportion of vivax and mixed infection patients who are correctly treated with TQ and PQ based on their G6PD result • 1.3. Proportion of vivax patients that are correctly treated with TQ based on the revised algorithm • 1.4. Proportion of vivax and mixed infection patient who are correctly treated with PQ based on the revised algorithm • 1.5. Proportion of vivax and mixed infection patients who are correctly treated with no or alternative radical cure regimens based on contraindications • 1.6. Proportion of vivax and mixed infection patients who attend a follow-up visit,at health facility at Days 2, 3, 4, 8, and by phone or home visit call on Days 15, [-1 day; +2 days] and 29, [-2 day; +2 days]	Quantitative	Individual patient Case Report Form
Secondary objectives:	**Secondary endpoint(s)**: • 2.1. Proportion of non-eligible patients that receive RC	Quantitative	Individual patient Case Report Form

2. Determine the capacity of the health system to safely implement RC after G6PD testing	• 2.2. Proportion of non-eligible patients that receive PQ • 2.3. Proportion of non-eligible patients that receive TQ		
	• 2.4. Total number of AHA identified during the study • 2.5. Proportion of patients experiencing AHA during follow-up period • 2.6. Proportion of all AHA identified by HCP during the study follow-up period	Quantitative	AHA report form and Individual Case Report Form, any other AHA reported to facilities and the study team
	• 2.7. Proportion of HCP who are able to correctly identify 8AQ- related Adverse Events	Training evaluation	Standardized assessment using a vignette-base test, used at pre-training, post training/ at baseline, midline, end line
3. Assess the quality and effectiveness of training and monitoring, and supervision strategies through competency testing, and training and supervision evaluations	• 3.1. HCP satisfaction of the training provided	Training evaluation and qualitative component	Training evaluation questionnaire (based on Likert scale) completed by HCPs after each training session Overall satisfaction explored through In-depth Interviews and Focus Group Discussion
	• 3.2. HCP knowledge and skills regarding G6PD testing and RC	Training evaluation and competency assessments	Standardized competency assessment (including self-assessments) used at pre-training, post training/ at baseline, midline, end line; Observations of HCP performing the test
	• 3.3. Number and frequency of supervisory visits conducted during the study duration per HF	Monitoring visits	HF routine monitoring visit reports

	• 3.4. Adherence to supervision Standard Operating Procedure (SOP) and implementation of any corrective actions identified through supervision	Monitoring visits and qualitative component	HF routine monitoring visit reports; FGD and interviews
	• 3.5. Proportion of HCP who received personal routine supervision in the past 6 months	Monitoring visits	HF routine monitoring visit reports
4. Explore barriers and facilitators to adding TQ to the treatment algorithm at national level within different case finding strategies	• 4.1. Health facility characterization	Monitoring visits	HF routine monitoring visit reports
	• 4.2. Patients and HCP perception of and experience with the new RC algorithm	Qualitative component	FGD and interviews
5. Determine the costs associated with introducing a single dose radical cure	• 5.1. Quantity and cost of G6PD diagnostic procured and used (total and per case)	Costing component	Micro-cost collection instruments / financial records
	• 5.2. Quantity and cost of TQ procured and used (total and per case)	Costing component	Micro-cost collection instruments / financial records
	• 5.3. Total cost of training sessions organized for HCP at study sites on G6PD testing and revised treatment algorithm	Costing component	Micro-cost collection instruments / financial records
	• 5.4. Total cost of G6PD diagnostic quality assurance and contribution to cost per case	Costing component	Micro-cost collection instruments / financial records
	• 5.5. Total and per patient monetary cost of including G6PD testing and single dose cure within routine malaria care from the perspective of the health system	Costing component	Micro-cost collection instruments

6.Monitor the frequency of malaria recurrences in study participants after first encounter treatment	• 6.1 Total number of recurrences identified in study participants until Day 29. • 6.2 Number of recurrences identified in study participants treated with TQ during until Day 29. • 6.3 Number of recurrences identified in study participants treated with PQ until Day 29. • 6.4 Number of recurrences identified in study participants treated with no RC until Day 29.	Quantitative	Patient contact through follow-up visits using a standardized questionnaire.
	•		
7. Monitor SAE in study *P.vivax* patients receiving RC	7.1. Number of *P. vivax* patients reporting serious adverse events after TQ and PQ administration until Day 29. 7.2. Frequency and severity of each serious adverse event reported after TQ and PQ administration until Day 29	Quantitative	Individual patient Case Report Form

Exploratory objective: 1. Monitor moderate and severe adverse events in study *P.vivax* patients receiving RC	1.1. Number of *P. vivax* patients reporting moderate and severe adverse events after TQ and PQ administration until Day 29. 1.2. Frequency and severity of each moderate and severe adverse event reported after TQ and PQ administration until Day 29	Quantitative	Individual patient Case Report Form

8 Study sites and participants

8.1 Study sites

As Vietnam is approaching elimination, its annual *P. vivax* caseloads are low and highly variable. According to the MoH's annual malaria data, the number of annual *P. vivax* cases in 2020 was 509 and in 2021 was 253 cases, and in 2022 was 169 cases, and in 2023 was 207 cases, and in 2024 was 70 cases across the country of over 90 million people and the five-year moving average of 2020-24was 242 cases (Annual national malaria data, accessed July 2024).

To mitigate potential biases resulting from non-randomization, criteria in our selection of study sites However, in order to select study health facilities, the support from local authorities is highly important; the agreement from provincial health departments, district health departments and local health authorities will facilitate the study implementation. Further, we plan that all cases captured by health facilities under our study site should be assessed for eligibility and exclusion criteria which will thoroughly be trained to participating health care workers during initial capacity building and continuously monitored during supervision visits. The researchers will also manage data quality closely by reviewing periodical submission of revised reporting forms, especially in earlier stage of the trial to promptly notice and resolve any issue in implementation.

The lowest level of facility-based care is provided at the commune level at commune health stations. Commune health stations are located within districts, which generally have one or more district health center. District health centers are where severe malaria cases or patients with other complications are referred to, including treatment for AHA with blood transfusion and/or dialysis. These districts are located within specific provinces.

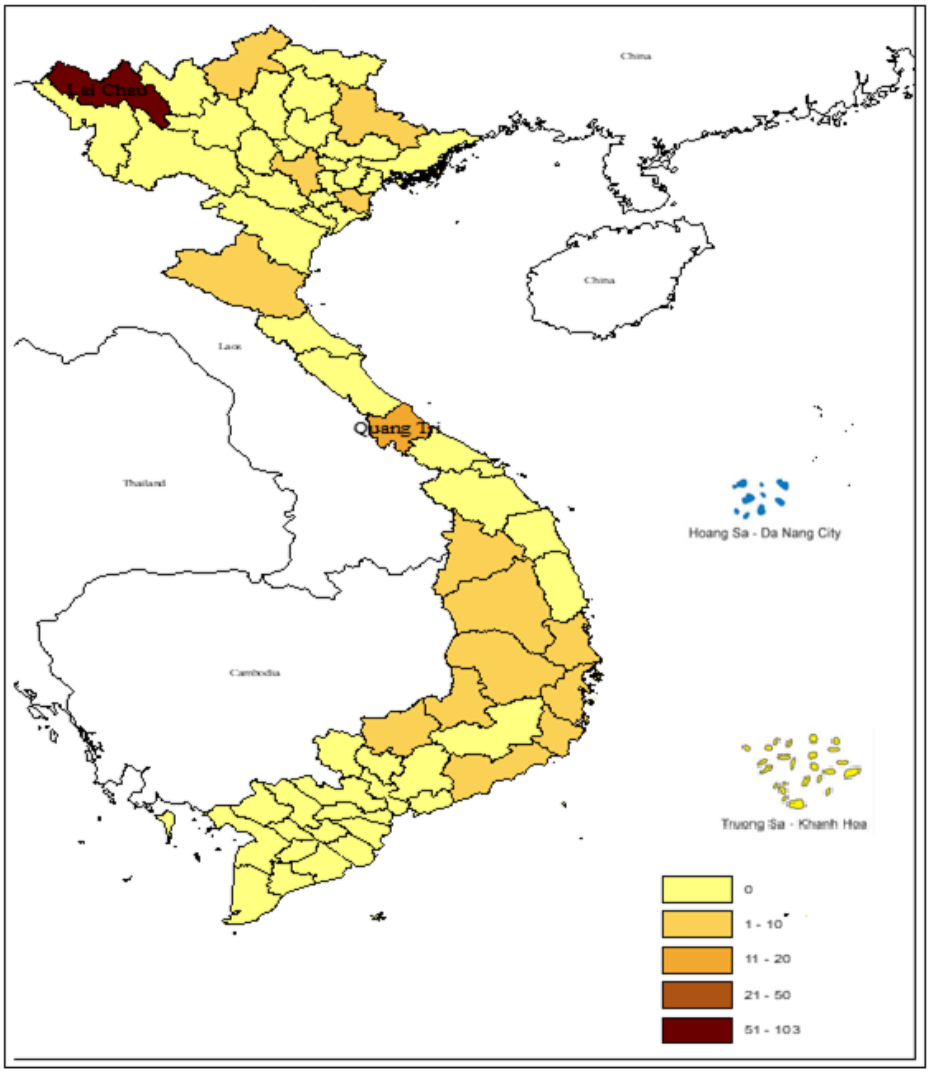
Health facilities are selected based on the following criteria:

Table 5: Criteria for site selection

Principle	**Criteria**
Sufficient vivax cases	Communes with ***P. vivax* cases** in last 5 years
Compliance with revised case management algorithm	**G6PD quantitative testing** in use (e.g., devices in good condition, consumables in stock, health staff been trained to use and interpret the result of the test, etc.)
Safety	For timely transfer and blood transfusion in case of AHA: - **Communes** whose boundary lies around within **50-km radius** from their direct DHCs. - **DHCs** are approximately **100-km distance** or less to their direct upper-level hospitals capable of blood transfusion
Leadership support	Support from **provincial leadership** to carry out the study
Representation across multiple districts	Approximately 6 districts will be selected to ensure that there is representation of diverse contexts within the malaria endemic areas of Vietnam.

These criteria will be applied to the data from the malaria program and sites will be prioritized accordingly. These data will be updated prior to study start to represent the most up to date malaria incidence available, including areas of recent outbreaks. As the *P. vivax* caseloads are highly variable, final decisions related to study sites will be determined prior to study start based on the above criteria national malaria data.

Figure 7: Annual* P. vivax *distribution in Vietnam, data per commune* (Annual national malaria data, accessed December 2022) *showing high heterogeneity and focalization.



The final list of study sites will be selected, based on the most recent data, from the following districts.

- 2-6 commune health stations in Muong Te district of Lai Chau province and Muong Te district health center
- 2-6 commune health stations in Bu Gia Map district of Binh Phuoc province and Bu Gia Map district health center.
- 2-6 commune health stations in Krong Pa district of Gia Lai province and Krong pa district health center.
- 2-6 commune health stations in Dak Doa district of Gia Lai province and Dak Doa district health center.
- 2-6 commune health stations in Son Hoa district of Phu Yen province and Son Hoa district health center.
- 2-6 commune health stations in Khanh Vinh district of Khanh Hoa province and Khanh Vinh district health center.
- 2-6 commune health stations in Huong Hoa district of Quang Tri province and Huong Hoa district health center

8.2 Study participants

P. vivax patients from 6 months old with *P*.vivax infection and *P*.vivax mixed infection and HCP who provide or supervise malaria services are the key study populations.

8.2.1 Inclusion and exclusion criteria for HCP

All HCP who provide malaria case management services will be asked to participate in the relevant trainings on the use of the new algorithm. Delegated healthcare workers are doctors/physicians and malaria focal points who meet the following minimum requirements:

- Licensed doctors or physicians who are:
    - In charge of malaria case management – especially *P. vivax* (including but not limited to reading diagnostic results, patient counseling, and medicine prescription) in the selected health facilities;
    - Familiar with current national malaria diagnosis and treatment guideline
    - Capable of interpreting results of G6PD quantitative diagnosis as confirmed by the health facility;
- Malaria focal points who are:
    - Assigned by the facility leaders to be in charge of coordinating malaria prevention and control activities and reporting malaria data in the district or commune;
    - Malaria program managers at provincial, regional, and national levels as needed

In case the doctor/physician is also the malaria focal point, s/he must meet the requirements for both roles as described above.

Assigned healthcare providers who meet minimum requirements above may undergo a training course on revised case management algorithms and enter a post-training knowledge-attitude-practice assessment. The training course and the assessments will be tailored according to the role of the participating health care workers (i.e., the doctor/physician's role or the focal point's role). Those who pass the test will be asked if they agree to participate in the study. Those who agree to participate by providing written informed consent will be included in the list of participating healthcare workers. A small number of healthcare workers will be selected at random for an in-depth interview via telephone to obtain more insights of their experience with the new intervention model.

8.2.2 Inclusion and exclusion criteria for patients

All patients who have a confirmed P. vivax or mixed infection as per the protocol over the age of 6 months at the facility or as part of ACD, either a positive RDT or microscopy, will be approached to participate in the study. This includes pregnant and lactating women, who have a contra-indication to both PQ and TQ, and will be excluded from RC, but for whom correct case management will be evaluated as part of the primary endpoints. Only patients providing informed consent and/or informed assent will be included. Those with signs of severe infection will not be approached for inclusion in the study as they are likely to be transferred to higher level facilities for management. In addition, prescription of TQ being contra-indicated with severe infections and with treatment with artemisinin derivatives, evaluation of the intervention package would not be possible for these patients.

8.3 Size of the study

8.3.1 *P. vivax* infected patients

The study size calculation was based on feasibility considerations and on the primary endpoint of the study. The study size was determined to ensure a satisfactory precision of this percentage, taking into account the low incidence of *P. vivax* in Vietnam.

The precision (e) of the 95% CI of a percentage (i.e., half of the width of the CI) is determined using the following formula:

$$e = 1.96 \times \sqrt{\frac{p(1-p)}{n}}$$

where p is the percentage and n the study size.

The following table presents the precision and the corresponding 2-sided 95% CI for a percentage of *P. vivax* patients treated correctly with RC and a study size ranging from 30 to 100 *P. vivax* patients.

Table 5: Precision and 95%CI Obtained for Percentages from 80% to 99% with Study Sizes from 30 to 150

	Percentage									
	80%		**90%**		**95%**		**97.5%**		**99%**	
N	**e (%)**	**95%CI**	**e (%)**	**95%CI**	**e (%)**	**95%CI**	**e (%)**	**95%CI**	**e (%)**	**95%CI**
30	14.3	65.7; 94.3	10.7	79.3; 100.0	7.8	87.2; 100.0	5.6	91.9; 100.0	3.6	95.4; 100.0
40	12.4	67.6; 92.4	9.3	80.7 ; 99.3	6.8	88.2, 100.0	4.8	92.7 ; 100.0	3.1	95.9, 100.0
50	11.1	69.9; 91.1	8.3	81.7; 98.3	6.0	89.0; 100.0	4.3	93.2; 100.0	2.8	96.2; 100.0
60	10.1	69.9; 90.1	7.6	82.4; 97.6	5.5	89.5; 100.0	4.0	93.5 ; 100.0	2.5	96.5 ; 100.0
80	8.8	71.2; 88.8	6.6	83.4; 96.6	4.8	90.2; 99.8	3.4	94.1 ; 100.0	2.2	96.8 ; 100.0
100	7.8	72.2; 87.8	5.9	84.1; 95.9	4.3	90.7; 99.3	3.1	94.4;100.0	2.0	97.0; 100.0
120	7.2	72.8 ; 87.2	5.4	84.6 ; 95.4	3.9	91.1 ; 98.8	2.8	94.7 ; 100.0	1.8	97.2 ; 100.0
150	6.4	73.6 ; 86.4	4.8	85.2 ; 94.8	3.5	91.5 ; 98.5	2.5	95.0 ; 100.0	1.6	97.4 ; 100.0

e: precision of the 95% CI.

For example, with 30 patients, the 95% CI for a percentage of 97.5% is [91.9%, 100.0%], and the precision 5.6%.

Overall, 30-150 eligible patients are estimated to be included in the study. This is based on an estimated 1-2 patients per facility at approximately 24 facilities, and an additional up to 30 patients identified through ACD. Due to the nature of elimination contexts, the total number of *P. vivax* patients is difficult to anticipate. Based on historical *P. vivax* caseloads, we anticipate a minimum of approximately 10 patients to be enrolled per month of study implementation. A minimum of 30-40 patients would allow for estimating the endpoint for the primary objective with adequate precision. A maximum of 150 patients will be enrolled to allow for estimating the endpoint for the primary objective with greater precision. as shown in table 5. Further, a key aspect of this study design is to allow sufficient duration of data collection to understand the intervention package implementation over time. A minimum of 4 months duration is anticipated. Recruitment will be monitored closely over the course of the study and the study team will consider options including increasing ACD campaigns as well as additional study facilities over the course of the study.

8.3.2 Health care providers

The HCPs are also a key unit of analysis for the study. We will recruit representatives from all health levels involved in malaria control and management for individual interview and focus group discussion as well as competency testing. We will approach all available HCP at participating Health Commune Stations for participation in the training and enrollment into the study. This will include about four per facility or up to 144 HCP. In addition to facility HCP and NIMPE team, we will plan to include up to 2 staff from provincial level and up to 2 staff from district level involved in ACD campaigns. This study will also include higher level malaria program supervisors. Those participants include 2-3 technical and program leaders (e.g., MoH), in each province we will enroll 2 local health care leaders (e.g., provincial CDC) and 1-2 representatives of district health facilities (e.g., department heads of the district health center). In total, up to 184 health care providers or key stakeholders involved in malaria case management will be enrolled for the purpose of collecting competency assessment and qualitative data.

Table 6: Composition of HCP and key stakeholders enrolled in study

No	Level of health facility (number of facilities)	Number of staff at each facility	Total staff at each level	Maximum anticipated enrollment
1	Commune Health station (14-36)	3-4	42-144	144
2	District health center (7)	1-3	7-21	21
3	Provincial CDC (6)	1 - 2	6 - 12	12
4	MoH/Central/regional level	7 - 10	7 - 10	10
5	International stakeholders	2	2	2
Total				189

The minimum number of patients and HCPs assumes all sites are active for the entire duration of study enrollment.

8.3.3 Qualitative assessments

The qualitative component, which will include key informant interviews and focus group discussions, will be conducted in all selected HFs and among those working in ACD. Targeted recruitment will be applied to include different views from health workers, patients, and other community members to reach maximum variation. At minimum, at least one health facility from each level, commune health station (where applicable), district health center, and hospital, will be included. Based on results of the training and HCP competency assessments, specific facilities may be selected based on whether they have a high or low degree of adherence to the revised case management algorithm.

The final sample size for the qualitative component will include up to 30 HCPs and up to 20 study patients. This will be a subset of HCP and patients already enrolled in the study. These participants will undergo a separate recruitment, consent, and enrollment process, using specific consent forms. Patients, including caregivers of minor patients, will be identified after their participation in the study, based primarily on which health facility they attended, as health facilities will be selected for inclusion in the qualitative assessments based on the description above. Patients identified from active case detection campaigns will be referred to nearby health facilities for recruitment, consent and enrollment in qualitative assessments. The study team will aim to recruit participants who participated in the study within 6 weeks of the qualitative assessments so as to mitigate the risk of participants forgetting key aspects of their participation.

Interviews and focus group discussions will conclude when saturation is reached, or when each qualitative interview produces only largely previously discovered data. A detailed sampling frame will be developed in advance of the study start.

9 Endpoint measures

9.1 Measures of adherence to the revised case management algorithm

The primary objective of the study is to determine the level of adherence to the revised case management algorithm at the patient and provider levels.

The primary endpoint related to this objective is:

- the proportion of vivax patients who are correctly treated with RC based on the revised algorithm. It will be computed as follows:

$$1 - (\frac{yt + yp + ya + ym}{Y})$$

Where y_t== number of G6PD deficient (G6PDd) and intermediate (G6PDi) cases who receive TQ + number of cases with unknown G6PD status who receive TQ + number of G6PDd and G6PDi cases who receive wrong dosage of PQ

y_p == number of non-eligible pregnant / breast-feeding women who receive either TQ or PQ

y_a == number of patients below 16y who receive TQ + number of patients below 6 months who receive PQ

y_m== number of patients who are prescribed TQ after having been treated with an ACT for the blood stage infection

Y == total number of patients who receive either TQ or PQ

This endpoint will be further disaggregated in sub-endpoints to look specifically at the proportion of patients who are correctly treated with RC (either TQ only, or PQ only, or both) based on their G6PD level, and disaggregated in different case finding strategies.

- The proportion of patients who come back for a follow-up visit

This endpoint will be computed by calculating the ratio between the number of patients who attend their follow-up visit and the total number of patients included in the study and that receive at least one dose of treatment. Patients presenting outside of the visit window (-1 days or + 2 days after treatment start) will not be counted in the numerator. Patients who experience an AHA or SAE and present at the facility earlier than day 3 will not be counted in neither the numerator nor the denominator. It is assumed that RC starts on day 1.

9.2 Measures of secondary objectives and additional endpoints

In addition to the above primary objective and related endpoints, the study also includes secondary objectives as described below.

9.2.1 To determine the capacity of the health system to safely implement RC after G6PD testing in different case finding strategies

To achieve that objective, the study will rely on both quantitative endpoints and process indicators. The quantitative endpoints are:

- The proportion of non-eligible patients that receive RC.

  This endpoint will be computed using the following formula:

$$\frac{xt + xp + xa + xm}{X}$$

Where x_t== number of G6PDd and G6PDi cases who receive TQ + number of cases with unknown G6PD who receive TQ

x_p == number of non eligible pregnant and breastfeeding women who receive TQ

x_a == number of patients below 16y who receive TQ

x_m== number of patients who are prescribed TQ together with an ACT

X == number of cases who receive TQ

As the study population only includes confirmed vivax patients, the above formula does not include non-vivax patients who could accidentally receive TQ.

This endpoint will be further disaggregated in the sub-endpoints to look specifically at the proportion of non-eligible patients who receive TQ or PQ (see Table 4). We will also look at specific reasons for patients being categorized as incorrectly treated and looks at differences in this endpoint across case-finding strategies.

- The total number of suspected or confirmed AHA identified during the study

Cases of suspected or confirmed AHA detected during the study will be described and counted.

The process for detecting AHA and collecting additional information is further described under sections 11.1 Data management and 13.3 Patient Safety Oversight.

- The proportion of patients who experience AHA during the follow-up period in each case finding strategy

This endpoint will be computed as follows:

$$\frac{n_{AHA}}{\mathrm{N}_{FU}}$$

Where n_{AHA} == number of patients experiencing AHA

N_{FU} == number of patients from which FU visit is available

- Proportion of all AHA identified by HCP during the study follow-up period

This endpoint will be computed as follows:

$$\frac{n_{HCPAHA}}{\mathrm{N}_{AHA}}$$

Where n_{HCPAHA} == number AHA identified by HCP during the follow-up visits

N_{FU} == number AHA identified at any point in time during the study

- Proportion of HCP who can correctly identify 8-AQ-related AHA

All HCP working in study facilities will be trained on detecting and reporting 8-AQ-related AHA. In addition, job aids and working instructions will be developed and made available in all study facilities. The ability of HCP to correctly identify those events will be evaluated through standardized assessment using a vignette-base test. The vignette-based test will be conducted immediately after the initial training, and up to two occasions afterwards.

9.2.2 Assess the quality and effectiveness of training and supervision strategies through competency testing, and training and supervision evaluations

To achieve that objective, the study will evaluate several dimensions and rely on both process indicators as well as qualitative assessments. The following endpoints will be assessed:

- HCP satisfaction with the training provided

HCP satisfaction will be evaluated through a simple questionnaire using a Likert scale, to be completed after each training session. Overall satisfaction will also be explored through In-depth Interviews (IDI) and Focus Group Discussion (FGD) (see section 7.6 Qualitative component).

- HCP knowledge and skills regarding G6PD testing and RC

All relevant HCP working in study facilities will be trained on the relevant aspects of performing the G6PD testing, interpreting its result, evaluating patient's eligibility for RC and choosing the appropriate treatment as per their role accordingly (See section 13.1.3 Training). In addition, job aids and working instructions will be developed and made available in all study facilities. HCP knowledge and skills regarding G6PD testing, and RC will be assessed through standardized competency assessments (including self-assessments) at three time points during the study 1) post-training, mid-line and endline.

Observations of HCP competency in the revised treatment algorithm may be conducted, at different points during the study in a sub-set of facilities. These observations may include the use of the G6PD test using control reagents or discard samples, the application of the treatment algorithm using real or contrived results, and counselling messages delivered to patients based on real or contrived diagnoses. The study monitoring team will conduct these observations as part of regular assessment visits.

- Number and frequency of supervisory visits conducted by the NIMPE during the study duration per HF

Prior to study start, the nature of the existing supervision program will be assessed and characterized in all study facilities. For instance, the usual frequency and quality of supervision visits from regional malaria program focal points will be evaluated (2-4 visits per year). After study start, the continuity in this supervision program will be evaluated through regular monitoring visits. The number of supervision visits conducted throughout the study period will be recorded.

- Proportion of HCP who received personal routine supervision during study conduct

To complement the above endpoint, the proportion of HCP who have received personal routine supervision during the study will also be measured. This will be evaluated at one timepoint, towards the end of the study.

9.2.3 Explore barriers and facilitators to adding TQ to the treatment algorithm at national level within different case finding strategies

There are several contextual factors and aspects of the intervention implementation strategy, at the patient, provider, and facility level, that may act as either barriers or facilitators to the implementation of the revised vivax treatment algorithm. To understand these factors, the study will evaluate several dimensions and use on both process indicators as well as qualitative assessments. The following will be explored:

- HF characteristics and capacities that either facilitate or hinder the roll out of the implementation package and its different components
- Health workforce characteristics that influence the correct use of RC algorithm
- Patients and HCP perception of and experiences with the new RC algorithm: this will be evaluated as part of the qualitative component (see section 7.6 Qualitative component)

9.2.4 Determine the costs associated with introducing a single dose RC

The following costs will be considered in the analysis.

- Quantity and cost of G6PD diagnostic procured and used (total and per case)
- Quantity and cost of TQ procured and used (total and per case)
- Total cost of training sessions organized for HCP at study sites on G6PD testing and revised treatment algorithm

- Total cost of G6PD diagnostic quality assurance and contribution to cost per case
- Total and per patient monetary cost of including G6PD testing and single dose cure within routine malaria care from the perspective of the health system

The cost implications of introducing G6PD testing before RC, including a single-dose cure, within routine care will be assessed. The key cost drivers have been identified and will be validated with the MoH and /or local health authorities. This will help ensure that all relevant cost information required for budgeting purposes, is collected and appropriately defined.

Costing data which will be collected will inform the development of a value proposition for policy adoption. Individual patient cost data will not be collected. The data collected in these studies may also contribute to secondary cost effectiveness assessments.

Examples of the types and potential sources of expenditures are shown below and will be refined during the process mapping activity.

Table 7: Examples of types and sources of expenditures

Training		
Category	**Types of expenditure needed**	**Potential sources of information**
Service	• Room rental • Training materials/books • Travel/transit costs • Tea break/lunch costs • Per diems	• Purchase receipts • Training logs • Travel records • Financial records
Commodities	• G6PD diagnostics costs (device, consumables, and controls) • Additional consumables needed for a blood draw • Printed training materials	• Purchase receipts • Training logs • Financial records
Case management		
Category	**Types of expenditure needed**	**Potential sources of information**
Commodities	• G6PD diagnostics costs (device, consumables, and controls) • G6PD diagnostics repairs/support • Additional consumables needed for a blood draw • Cost of single dose RC • Cost of PQ • Printed materials	• Stock cards • Quality assurance log book • Financial records. • Issue logs with national malaria program/study staff

9.2.5 Monitor the frequency of recurrences in study participants after first encounter treatment up to Day 29.

To achieve that objective, the study will rely on quantitative endpoints as follows:

- Number of patients reported the malaria episode up to day 29 after first treatment in total and stratified by treatment type.
- Patients will be encouraged to return to the same health center facility if they experience malaria symptoms and will be monitored by microscopy.
-

-

9.2.6 Monitor the safety in *P.vivax* patients receiving RC

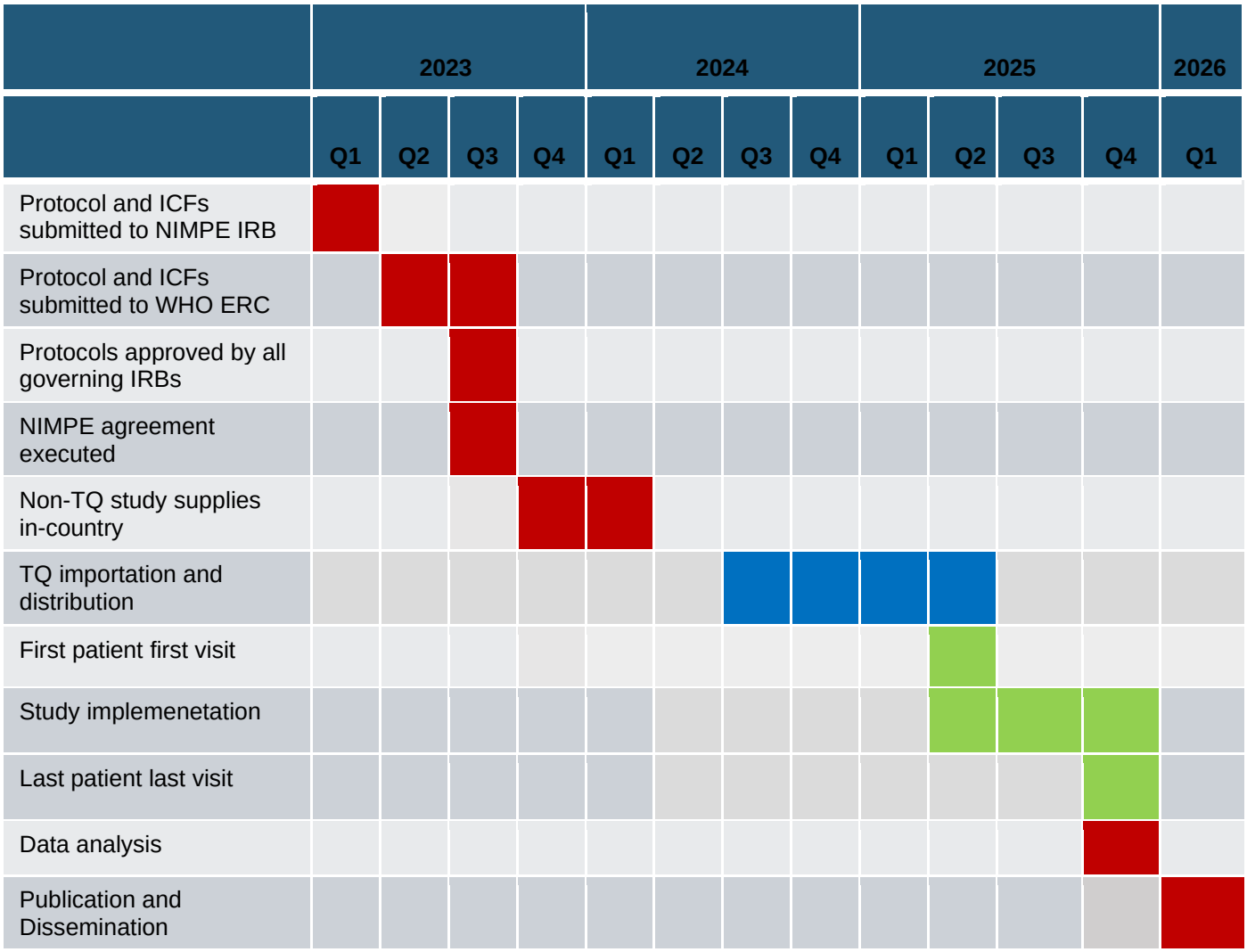
To achieve this objective, patients enrolled in the study will be followed-up for 29 days. This will include a mix of in-person visits as recommended by national treatment guidelines as well as phone follow-up visits. At each visit, standard practices including assessing clinical symptoms/signs will be done, as well as running the relevant lab tests, such as a blood slide to assess treatment failure, will be conducted. Any moderate, severe, or serious adverse events will be noted in the patient medical records as well as study-specific case report forms. Patients will be checked and monitored at health facilities for adverse events from Day 1 through Day 4 and on Day 8. On Days 15 and 29, HCPs will call the patients or visit the patient at home to monitor the course of treatment.
The number of patients reporting SAEs/AHAs after TQ/PQ administration will be enumerated as well as the frequency and severity of each SAE/ AHAs.

Separately, the number of patients reporting moderate/severe AEs after TQ/PQ administration will be enumerated as well as the frequency of each moderate/severe AE.

10 Study schedule

The detailed study schedule is described in Figure 8.

Figure 8: Estimated timelines for study implementation



11 Data management and analysis

11.1 Data management

The different objectives and methods outlined in previous sections entail that study data will be collected through different standard forms and reports. The data collection tools to be used are summarized in Table 4 and detailed below.

Electronic databases will be designed to record all the data to be collected as per the quantitative components of the study. Only authorized, trained personnel will have access to this database. This includes data entry personnel, study sponsor staff (e.g., PATH), as well as staff from sponsor delegates.

Automated data checks will be built in the electronic database so that inconsistencies in the data and out-of-range values are flagged upon entry. In case of abnormal values, discrepancies or inconsistencies, the data entry personnel will query the study HF for clarification or correction. Any change or correction to the original forms will be documented appropriately.

After completion of data cleaning and database lock, the deidentified database will be shared with the key stakeholder including the National Malaria Control Program and other national implementation partners in accordance with the data sharing agreements in the respective agreements and contracts. The identifiable study data and documents will be kept under restricted and secured access by NIMPE up until 5 years after study end. After this retention period, study data and documents will be destroyed.

11.1.1 Adherence component

The quantitative endpoints will be informed by data collected through the following study forms:

- a CRF completed for each individual patient
- an AHA report form to be completed for every suspected or confirmed AHA, and either an AE or SAE report form will be additionally completed for reporting to the pharmacovigilance system .
- an SAE report to be completed for every confirmed SAEs

Data will either be directly collected in study-specific forms and transcribed from existing forms currently in use in the study facilities. HCPs enrolled in the study and members of the ACD teams will be responsible for data collection. Prior to study start, all HCPs at participating facilities will be trained on how to fill in the study-specific forms. Data collection in the AHA and SAE report form will be under the responsibility of the PI and his/or delegate.

Paper case report forms (CRF), SAE and AHA forms will be used, and those will be collected at regular intervals by dedicated study staff. The data contained within these paper forms will be entered into a dedicated study database by trained data entry personnel.

11.1.2 Qualitative study

Study data will be collected through in-depth interviews (IDIs), and FGDs. An adapted implementation framework will be used to guide the development of questionaries and data analysis. FGDs will be used to review some of the processes and discuss how to improve them. IDIs will be used to investigate a topic in depth with key informants. In-depth interviews and FGDs will be recorded, transcribed, and translated in English. In informal conversations, or on occasions where participants do not want to be recorded, written notes will be used to generate a summary. The

recordings will be stored under restricted access according to local policies, for a minimum period of 5 years after study completion. After that period, they will be destroyed.

11.1.3 Costing component

Key potential cost drivers have been identified through previous research and through discussion with key stakeholders. This will subsequently be validated with the national malaria control program and/or local health authorities prior to study start to ensure that the costs reflect those required for budgeting purposes. These costs included primarily the cost of commodities and the cost of training.

Standardized cost data-collection instruments will be developed with clear definitions and instructions regarding how the costs should be calculated, what should / should not be included, as well as preferred data sources. Objective data sources, such as invoices, training logs and payment, will be used whenever possible. Data will be collected prospectively as activities such as trainings and as commodities are ordered and used. Sources will be carefully recorded so that the costs can be validated. This will ensure consistency in data collected across multiple sites.

All costs will be calculated in local currency to minimize the impact of exchange rate fluctuations. The cost per patient will be evaluated by considering the cost of the commodities used for that patient (including any additional tests needed for re-testing and quality assurance) as well as health system costs such as supervision. The training costs will be a one-off cost. These monetary costs will be considered separately, over the course of the study period.

11.1.4 Recurrence component

All data for the assessment of recurrences will come from the CRF completed for each patient as well as the associated CRFs for follow-up at day 29. Confirmed P. vivax recurrences observed through day 29 will be summed by participant and stratified by treatment received.

11.2 Data processing and analysis

11.2.1 Statistical analysis for the adherence and recurrence components

The primary objective of the study is to assess feasibility of introducing RC algorithm to routine case management of vivax patients. The primary endpoint for this is adherence to the revised case management treatment algorithm, measured at patient level. Frequency tables and summary statistics for all data points that feed into the algorithm alongside potential confounding factors and stratifying variables of interest will be initially presented. The data will be processed to obtain estimates of the primary and secondary endpoints and corresponding 95% confidence intervals.

The proportion of all cases correctly treated as an aggregate and within each of three case finding strategies will then be obtained. The reason for incorrect treatment with PQ/TQ will be tracked down the line of the treatment algorithm to identify the parameter overlooked by HCP e.g., G6PD status, age, malaria type, etc.

As part of the recurrences component, the difference between recurrences reporting during the follow-up period among study participants who receive TQ will be compared to recurrences reporting during the follow-up period among study participants who receive PQ. This may be compared to anonymized, aggregate, historical data at the facility level, where these data are available and considered reliable. Similarly, the number of study participants who received TQ and present again to the facility with a recurrence during the follow-up period will be tracked and compared to the number of study participants who received PQ and present again to the facility with a recurrence during the

follow-up period. The endpoints for this component will be included in the study analysis plan, described below; however, given the limitations of these data, no statistical tests will be conducted.

A statistical analysis plan (SAP) will be developed and finalized before database lock for analysis, based on the endpoints outlined above.

Every effort will be made to keep the amount of missing data as small as possible, by the implementation of checks into the electronic CRF, close data monitoring and training of the relevant study personnel. If, despite these efforts, there is a certain amount of missing data, additional analyses may be carried out to take this into account. These will be addressed in more detail in the SAP.

11.2.2 Analysis for qualitative component

A deductive approach using content analysis will be used to identify emerging themes from IDIs and FGDs. Coding frameworks will be developed *a priori* using the overarching logic model and modified and added to as new themes on the use, perceptions and experiences of the treatment algorithm emerge. Analysis will be conducted concurrently with data collection in an iterative fashion.

11.2.3 Cost evaluation

The costing component will consider the financial costs to introduce G6PD testing as part of this intervention and the revised treatment algorithm, including the single dose radical cure, at the study sites and compared across case finding strategies in order to inform future budgets or funding requests. The focus of the analysis is to describe the additional costs associated with incorporating G6PD testing into routine *P. vivax* case management that would not occur otherwise, not the cost of routine G6PD testing with PQ that is already part of national guidelines. Data on financial costs will be collected to describe training and routine case management within two categories: service and commodities.

- Training costs will be collected during the study training and disaggregated within the three categories of personnel, health service, and commodities. Total training costs will also be aggregated and divided by the number of health care staff trained and health facilities in attendance to provide cost measurements to the national malaria control program that could be used to estimate scale-up costs beyond the study facilities.
- Case management, or patient care, cost data will be collected routinely during the study within the quality assurance and commodities categories. Total costs at each facility and as part of each campaign will be divided by the number of *P. vivax* patients seen at that facility or during the campaign to estimate per patient costs. The same will be done in aggregate across all facilities and campaigns with all study patients to obtain a study-wide average cost per patient of G6PD testing and the revised treatment algorithm.
- The incremental routine patient care costs will include 1) the total costs and per case cost of the commodities (G6PD tests and single dose treatment), 2) the total costs of G6PD diagnostic quality assurance and contribution to per case cost. 3) The costs of training and supervision as well as the cost to integrate G6PD testing into active case detection. The data will be derived from micro-cost collection instruments / financial records.

12 Ethical considerations

12.1 Ethical framework

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza, 2013 and the International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences (CIOMS), 2016).

12.2 Ethical committees

The study protocol, the informed consent documents and the data collection tools will be submitted to the WHO Ethics Review Committee (WHO ERC). In addition, these same documents will be submitted to the Institutional Review Board of NIMPE

The study will not start in any facility before written approval by all relevant ECs has been obtained.

Any substantial amendments to the protocol or the Informed Consent Form (ICF) will also be submitted for approval to the same ECs/IRBs and competent authorities and will be implemented only after approval has been obtained.

12.3 Risks and benefits

The target population of this study includes

- HCP responsible for the treatment of malaria patients, including those involved in ACD, and working in study facilities during the study conduct
- Patients with a confirmed diagnosis of *P. vivax* infection presenting at one of the study facilities during the study conduct

12.3.1 Risks and benefits for HCPs

The goal of this study is to evaluate the operational feasibility of providing RC after G6PD testing, to inform the introduction of a revised treatment algorithm and improve patients' access to best clinical practice. HCP are a pivotal component of the operational feasibility question, and the implementation package has been designed to facilitate change in their practice and provide the support they require to conduct their work. Through a consultative, iterative process, this implementation package will be refined to incorporate HCP experience and views, and to address the challenges they encounter in applying the revised treatment algorithm. The study will provide a long-term benefit for all HCP managing vivax patients in Vietnam and in respective countries, as it will generate a package of interventions tailored to their needs, draw lessons from real-world implementation and ensure scale-up is smooth and efficient. In addition, individual HCP participating in the study will benefit from direct feedback on their performance, as well as access to job aids and training.

The main risks related to participation relates to possible adverse consequences for HCP, should their performance have an impact on their employment. HCP may be exposed to social risk, including reputational or professional harm. Mitigations to these risks include the following: prior to study start, information sessions will be held with facility managers and supervisors to highlight the necessary learning curve that HCP will go through, and stress that individual HCP adherence to the revised algorithm should not be used as an indicator of overall HCP performance. At beginning of the study, the processes for seeking informed consent and for ensuring data confidentiality will be discussed with HCP representatives at selected facilities. Those processes will be refined prior to study start, and measures will be put in place to protect confidentiality of HCP data (see section 12.6 Privacy and Confidentiality).

Participation in the study will not incur any additional cost to HCPs. As HCPs are expected to carry out additional tasks as part of their participation in the study (e.g. consent patients, collect data in dedicated study-specific forms), appropriate compensation will be discussed and agreed upon during study planning.

12.3.2 Risks and benefits for patients

Participation in the study bears minimal risk for individual patients compared to routine clinical management. The RC algorithm have been thoroughly evaluated and proved to be well tolerated and effective in clinical trials. In addition, initial experience from similar, on-going feasibility studies in Brazil, Thailand and Peru show that the algorithm can be used safely under real-world conditions.

Patients visiting study facilities during the study conduct will benefit from G6PD screening prior to RC. With respect to the risk of AHA in patients with G6PD deficiency, this risk is lower in the study compared to facilities or case management with no access to G6PD testing. All *P. vivax* patients attending the study facilities or ACD will be tested for G6PD deficiency prior to treatment. This means that the risk of AHA in the study is expected to be lower than under routine care. TQ has a long half-life, and since it is a single dose treatment, it cannot be discontinued, unlike PQ. During TQ development, no clinically significant AHA events were observed in patients with G6PD values ≥70%. Decreases in hemoglobin levels were reported, however in the clinical studies none of these events were deemed clinically significant and none required blood transfusion. There may be a residual risk related to the incorrect interpretation of the G6PD test, and to mitigate for this residual risk, study facilities will be selected based on the availability of blood transfusion services in near-by hospitals and availability of a functioning referral system. The follow-up visit scheduled at Day 2,3, 4, 8 and Day 15 will allow HCP to identify such risk and act accordingly. In addition, sub-set of endpoints and indicators that are likely to have consequences for patient safety will be monitored throughout the study, and corrective actions will be taken if required (see section 13.3 Patient Safety Oversight).

The study will provide a long-term benefit for all *P. vivax* patients and their communities in the respective countries, as its long-term objective is to improve quality of care and support shift to best clinical practice. Findings from this study will also be informative for other non-study countries and may contribute to improved diagnosis and treatment of vivax patients globally. The evidence generated by the study, as well as the lessons learned throughout its planning, conduct and reporting, will support revision of national treatment guidelines and inform the development of the national implementation strategy for the roll-out of the RC algorithm. Learnings from the study will allow the MoH to plan for the scale-up of the RC algorithm. Study outputs include a set of tools (e.g. training material, revised algorithm, patient counselling material), that will be ready-to-use by MoH.

Study-specific risks relate to the collection of additional data for research purposes. Measures will be put in place to protect confidentiality of patients data (see section 12.6 Privacy and Confidentiality).

Participation into the study will not incur any additional costs to patients. The G6PD test will be provided free of cost to all patients visiting the study facilities and included in ACD during the study duration, irrespective of whether they agree to participate or not; TQ will only be provided free of cost for eligible patients. PQ, as well as other malaria commodities (e.g. RDTs) will be provided free-of-cost either by the Ministry of Health (MoH) or covered by the patient's insurance, as per routine practice. Also transport costs for attending follow-up visits, for travelling to referral hospital for further diagnostic testing and for attending qualitative assessments interviews will be reimbursed to study patients. Any suspicion or confirmation of AHA or any SAEs requiring referral to higher-level hospitals will be followed-up and entirely paid for either by the study for all eligible patients.

12.4 Community engagement

This study includes a community engagement component, which takes into consideration the local context as well as cultural and societal norms in Vietnam. The aims are

i) to engage in a dialogue to harness local knowledge and HCP and patient insights towards better study preparation, local adaptation of the implementing package, recruitment and retention of participants

ii) to build a positive foundation of understanding, acceptance and support, at all levels, in order to ensure successful study conduct and smooth transitioning of new practice into routine care

iii) to build on priority initiatives of the NIMPE and local malaria program officials, including village health workers (VHW) who play a key role in public health messaging and community engagement

During the pre-study phase, activities encompassing good participatory practice will be conducted with the following objectives:

- facilitate community input into selected aspects of study documents, particularly training materials and patient information
- enable dialogue about concerns and benefits for the individual, community and vivax patients globally
- actively demonstrate transparent and ethically sound study planning and conduct
- inform about study rationale, timings, implications and hopes for outcomes

The study protocol will be reviewed by representatives of NIMPE. This study represents an extension of ongoing technical assistance and partnership between PATH, NIMPE, and the MoH across vivax malaria radical cure and other aspects of malaria elimination. NIMPE has a long-established working relationship in key study areas and health facilities will be oriented to the study aims prior to participation. During the study planning and start-up, training materials and patient counselling materials will be shared with members of community organizations supporting malaria service delivery in the region. Village Health Workers will be engaged in the research activities, both from a perspective of advising on study implementation as well as participating in aspects of the patient follow-up.

During the study, mechanisms will be developed to ensure effective communication with the community regarding the overall progress of the study, potential problems arising during the course of the study and solutions proposed to address them. Study participation will be closely monitored and if the participation rate is found to be low, reasons for this will be explored and addressed in collaboration with HCP representatives, VHWs, facility managers and local authorities.

During the post-study phase different communication channels will be used to inform the community about the study outcomes. This may include public meetings, and distribution of printed reader-friendly material to health facilities. In addition, the use of local media will be considered for result dissemination. Study outcomes will be posted on the *P. vivax* malaria study database to ensure transparency. Prior approval by local authorities for any such activities will be sought, where required.

12.5 Informed consent

12.5.1 Informed consent process

The process of obtaining informed consent in implementation research differs significantly from traditional consent in clinical trials (Gopichandran *et al* 2016; Edwards SJ, 1999, BMJ). In this

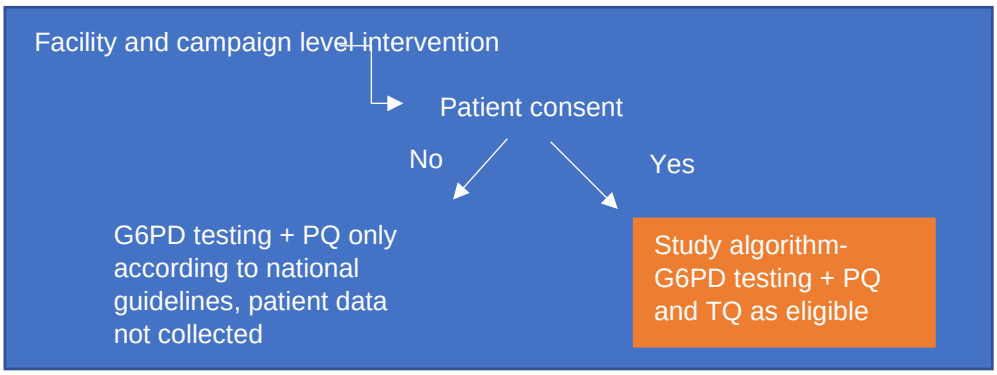
study, due consideration has been given to existing ethical guidelines for informed consent in Cluster Randomized Trials (CRT) and studies using cluster-level interventions (Weijer *et al* 2012). A two-level consent process is foreseen: permission for the introduction of the implementation package will be sought from the provincial health department in the province where the study is conducted, while consent for the collection of additional data for research purpose will be sought from individual HCPs and patients.

The justification for the above process is the following:

- The implementation package, including the use of a G6PD test as well as patient counselling, training and supervision, as well as patient follow-up visits will be rolled out *at facility level*. This entails that all HCPs working in a given study facility and as part of an ACD campaign will be trained and will be asked to revise their current practice and use the revised treatment algorithm. Consequently, all vivax patients that attend the study facility will be diagnosed and treated as per the revised algorithm. However, individual patients who do not consent to participate in the study will not be provided with TQ. Only patients who enroll into the study will be given TQ, if eligible. Patients who are seen at participating health facilities but who do not consent to participate in the study will be given PQ only, in line with current national treatment guidelines
- In addition, as recommended by WHO, patient's G6PD status should be determined prior to RC. This corresponds to best clinical practice and improves patient safety. Providing access to the G6PD testing only to patients that have consented to be part of the study would introduce a parallel system of higher quality care for study participants and poses ethical concerns.
- Managing multiple patients' pathways in study facilities will prove extremely challenging and would risk generating confusion from the HCP as to when to apply the revised algorithm and when not, ultimately leading to errors that could potentially affect patient safety. In addition, it would likely undermine the ability of the study to answer relevant research questions.
- The benefits of applying the revised algorithm and ensuring proper patients counselling and follow-up outweigh the risks and burden to patients and HCP. Both the G6PD test and the RC drugs have been thoroughly evaluated, approved by regulatory authorities, and will be used as per the approved indication
- Patients will be provided full information about the status of TQ and PQ

The facility and individual level interventions will be implemented as follows:

Figure 9: Facility/ campaign and individual level interventions



Facility level intervention to include training of all HCP, G6PD testing for all vivax positive patients, and follow-up

The autonomy of individual HCP and patients will be preserved. For HCP and patients who decide not to be part of the study, data will not be collected in study-specific forms but will only be entered into routine forms as per routine practice.

Individual HCP and patients will be free to withdraw from the study at any point in time, without this affecting the quality of care provided nor the job security of the HCP. Withdrawal will be documented and only data collected up until the date of withdrawal will be used in the analysis.

For children from 6 months to less than 8 years old, consent from either parents will be obtained; for children from 8 years to less than 18 years old, consent from either parents/guardian will be obtained in addition to the assent from children. For adult patients, they will give the consent for study participation by themselves.

Permission will first be sought from the provincial health department to implement the study in facilities falling under their directorate. Once this has been obtained, facilities managers and community representatives, including HCPs and patients' representatives, will be consulted. Meetings will be organized prior to study start to explain the purpose of the study, describe in detail the implementation package and data to be collected. Relevant community representatives will be consulted for feedback and input will be sought on the foreseen consent process and documents. Whenever required, consent documents will be modified, and additional material may be developed.

Individual consent will be sought from HCP for participation in the study. After the initial training, the study team will be responsible for explaining the purpose and objectives of the study and for describing what additional data will be collected to inform the study objectives. HCP will be given an opportunity to refuse to be part of the study. HCP consent will be documented through the HCP ICF. Two original ICFs should be completed, dated and signed personally by the HCP and by the study team. The HCP should be given one signed original form, the second original should be kept by the study team.

Individual consent will also be sought from patients for inclusion in the study and the use of their data for research purposes. A designated and trained HCP at the health facility will conduct the consent process. After confirmation of a vivax infection but prior to screening with the G6PD test, the designated HCP will explain the purpose and objectives of the study, the status of the tools used in the revised treatment algorithm, and for describing what additional data will be collected to inform the study objectives. It will be emphasized that participation is voluntary and that their decision will not negatively affect the care they receive in any way.

The potential participant will have the opportunity ask questions. Patients will be given an opportunity to refuse to be part of the study and that their data be collected to evaluate adherence to the revised algorithm. They will be excluded from the study population and data related to their G6PD status or treatment received will not be collected in study instruments. Patients' consent will be documented using the patient ICF and Informed Assent Form (IAF). Two original ICFs will be completed, dated and signed personally by the patient or his/her parents and/or legal representative and by the designated HCP. In addition, for minors able to give assent, two original IAF should be completed, dated and signed personally by the patients and by the designated HCP.

For the qualitative assessments, consent will be undertaken by members of the study team in a private setting in the health facility who will also conduct the qualitative assessment during site visits. The autonomy of potential participants will be ensured through a separate consent process, with specific terms that outline how participants can participate in the primary study without participating in any qualitative assessments. Further, members of the study team, rather than health care providers, will conduct the consent process. For the qualitative assessments, specific consent will be sought from participants to record their answers.

When appropriate, a conversational style oral presentation of consent information will be made in local language to participants to account for any difficulties understanding written consent forms due to low literacy. It will be ensured that a translator is present for patients who do not understand Vietnamese fully. Parent permission will be obtained for all participants under the age of 18. Child assent will be obtained for all participants at the ages of 8 to 17. Children aged 8-17 will express their assent in writing in the presence of their parent as a witness, to ensure the assent process is without any coercion.

If a potential participant is illiterate, an independent, impartial literate witness will be asked to join the consent process. This witness will be a health care worker or other family member/neighbor uninvolved in the study. The witness will read the consent form aloud to the potential participant and the witness will verify that the information read aloud matches the information written on the consent form. The witness will affirm that the study participant chose to be in the research study, that he or she was present the whole time the study was being explained, and that the participant had a chance to ask questions. The participant will get a copy of this form to keep. The witness will also sign the consent form.

12.5.2 Informed consent and assent forms

Informed consent and assent forms have been developed and translated into Vietnamese which consider cultural norms and literacy levels.

12.6 Privacy and Confidentiality

Privacy of HCPs will only be partially ensured in the study, as it would be impossible to not disclose that an individual HCP is taking part in the study. For instance, participating HCPs will be filling in study-specific forms to inform the quantitative endpoints and this will happen in the facilities premises used for routine care. However, the following measures will be put in place:

- to the extent possible, consent will be sought from HCPs in private locations.
- In each study facility, the study team will be responsible for recording the HCP personal details and HCP unique study number for all HCPs that have agreed to participate in the study in a dedicated list. To ensure privacy, this list will be maintained with access restricted to authorized study staff.
- All training reports, data collection tools, monitoring visit reports and administrative forms will be using the HCP unique study number. Names will not be used on any of these documents.

Privacy of patients will be ensured fully during the study. Consent will be sought from patients in private location in each facility. The HCP will be responsible for recording patients' personal details and patient unique study number for all patients who have agreed to participate in the study in a dedicated list. To ensure privacy, this list will be maintained with access restricted to authorized study staff. All data collection tools, monitoring visit reports, AHA, SAE report forms and administrative forms will be using the patient unique study number. Names will not be used on any of these documents and the study team will be responsible for ensuring all documents are anonymized before being transmitted to the study sponsor.

The study database will be secured with password-protected access systems and only accessible to dedicated data entry personnel. Special care will be taken to ensure that individual HCP performance data (e.g. competency testing score, data from individual CRF) is not accessible to

neither the facility manager or their supervisor. This will be essential to mitigate for any risk of adverse consequence related to poor performance (see section 12.3 Risks and benefits).

12.7 Dissemination of study findings and post-study access

The results of this study will be written up in dedicated study reports, which will form a basis for development of scientific publications. The publications will be submitted to peer review journals.

As indicated under section 18 Finance and Insurance this study falls under a Unitaid-funded project and co-funded by the Bill and Melinda Gates Foundation (BMGF). This project also includes a specific workstream aimed at translating evidence from the study into national policy, and achieve long-term, sustainable impact in target countries and beyond. Post-study access plans will be developed and will help create the conditions for access to the services and country scale-up through various activities to be co-developed with and/or validated by MoH. The plans will be grounded in study results and lessons learned, starting with the translation of evidence for use by policy makers, specifically by disseminating of study results in national and international meetings and events, collating, and sharing other relevant local/regional evidence, as well as through organizing and/or fostering regional and global *P. vivax* meetings. With a consolidated evidence pack, the project will aim to support policy change for the adoption of new tools (i.e., updating national treatment guidelines and other key documents/systems). Since all activities to be carried out by MoH requires advance funding approval by the government, we plan to use study results of the costing component to co-develop national investment cases for the adoption of new tools for safer radical cure. For this, we will hold meetings with the MoH/ to first discuss existing available resources/financing to allow for tools' market entry to then draft said cases aligned to national context.

Results will be shared with involved communities, as part of community engagement plans outlined in section 12.4 Community engagement.

Should the MoH decide to integrate the new tools into revised policy recommendations, the learnings from the studies will be instrumental to prepare for implementation of these revised recommendations. The studies will generate outputs (e.g. training material, patient counselling material, areas requiring further strengthening) that will be critical for successful scale up and maximize patients' access to best clinical practice.

To help guide actual scale-up in country, the study will help identifying policy options and delivery models. Together with the MoH a roadmap, introduction strategy, and key resources (e.g., training materials, training curriculum, other) for national scale-up will be developed and validated with key stakeholders. Finally, we will provide implementation guidance for national scale-up, particularly on supply chain and pharmacovigilance, to help ensure a sustained and safe post-trial uptake of new radical cure tools.

13 Quality assurance and oversight

13.1 Quality framework

13.1.1 Quality standards

As indicated in 12.1 Ethical framework this study will be conducted in compliance with ethical principles set forth in the Declaration of Helsinki and in the CIOMS guidelines. This entails that processes and tools will be developed, to ensure the rights, safety and well-being of study participants are protected, and that data generated are credible. A pragmatic, risk-based approach will be used.

13.1.2 Quality Assurance

Study documents are aligned with highest scientific and ethical standards and good research practice. These have been reviewed by external, independent experts.

As part of the initial HF characterization, all available routine SOPs will be reviewed, and adherence to those SOPs will be evaluated. In case a HF is found not to comply with the existing, routine SOPs, refresh training will be organized in collaboration with the NIMPE and SOPs may be updated. This training could include for example thick blood smear preparation and staining, use and reading of malaria RDT, G6PD test and interpretation, and blood-stage treatment.

As part of the implementation package, job aids and working instructions will be developed to support the adherence to the revised algorithm and patient follow-up. Those will cover the performance of the G6PD test and its interpretation, as well as the identification of 8-AQ adverse effects.

All partners involved in the study have solid experience in running similar studies. NIMPE has a long track-record in malaria research in Vietnam and has been involved in multiple studies in support of the MoH's agenda. PATH has been conducting similar studies in other locations, including Peru, Ethiopia and had supported the G6PD study in Vietnam.

13.1.3 Training

Training will be provided on the performance of the G6PD test, its interpretation, treatment and on the identification and management of signs or symptoms of AHA (including the severity grading of signs/symptoms) and reporting of moderate, severe and serious adverse events. This training will be delivered in each study HF prior to study start. The medical staff of the referral hospitals will also receive training on the detection and management of AHA. Village Health Workers will be included in trainings relevant to their role in the study, specifically for patient orientation, engagement and follow-up.

Specifically, training on AHA will emphasize the following symptoms and signs:

- dark (Coca Cola colored) urine
- yellowing of skin and/or sclera (jaundice)
- pallor
- back pain
- breathlessness or shortness of breath (tachypnea)
- rapid heart rate (tachycardia)
- fever, fatigue, dizziness, nausea and/or vomiting

With respect to the reporting of AEs to the national PV system, training on national PV procedures and forms will be organized in collaboration with national PV stakeholders.

The study team will be responsible for organizing those trainings and for ensuring that study only starts after all relevant staff have been trained.

For each facility, a log of HCP enrolled in the study will be maintained by the person delivering the training. Whenever an HCP leaves the facility, his/her participation in the study will end. This will be captured in the log. Whenever a new HCP joins the facility, he/she will be trained on the revised case management as soon as feasible and approached for participating in the study. This training will be delivered by the study team or by another HCP working in the same facility and who has already been trained. If he/she agrees to be part of the study, his/her name will be added to the log. In that way, the

study teams will be able to monitor staff turnover and organize additional training sessions whenever required.

13.1.4 Study monitoring

Assessment visits will be conducted on regular basis throughout the study conduct. The purposes of these visits are twofold; one, to collect data on process indicators and evaluate HCP performance and two to conduct traditional monitoring of study activities such as:

- Monitor progress in study enrolment
- Verify consent has been obtained from all participants
- Verify completeness of CRF and collect them
- Verify compliance with the study protocol
- Verify that potential cases of AHA and SAE have been reported
- Verify that moderate and severe AEs have been recorded and reported according to PV guidelines.
- Verify that study supplies are available in sufficient quantities and are stored adequately
- Provide re-fresh training as needed

Study monitoring will be considered a separate and discrete activity, apart from collection of data related to the process indicators or other qualitative assessments. Depending on study logistics, these visits may coincide, however.

13.2 Study Oversight

Given the embedding of implementation research in real-world contexts, there is a need to separate what should be governed by current practices in each health system, and what should be mandated by the study protocol. In the present study, the implementation package is part of the study-specific elements, therefore the G6PD testing, and liver-stage treatment of vivax patients and the management of AHA and SAEs as well as moderate and severe AEs will be according to the protocol. However, the overall management of patients will follow routine practice and will fall under the responsibility of HCPs working in public facilities under the supervision of the NIMPE. This entails that the initial diagnosis of malaria, the provision of treatment for the blood-stage infection, for instance will be conducted as per routine practice, under real-world conditions.

The oversight foreseen in the study will focus on ensuring the study is run according to the protocol. This oversight will complement, but not replace, the regular supervision of malaria services as lead by respective regional Institutes of Malariology-Parasitology-Entomology. Two levels of oversight are foreseen:

- At global level: a Global Study Team (GST) has been established under the leadership of MMV, which will ensure oversight of all feasibility studies conducted under the Unitaid grant. Its focus is on technical/scientific oversight, global operations, and quality compliance. The GST ensures that the Master and country-specific protocols are scientifically robust and comply with requirements set forth in the Standards for Reporting Implementation Studies (StaRI) (Pinnock *et al* BMJ 2017;356:i6795). It also ensures that relevant ethics principles, quality standards and regulatory requirements in each country are complied with. For instance, the GST is responsible for ensuring all necessary authorizations, including from relevant ECs, are obtained by each study sponsor prior to study start and that any change to the study documents after study start is duly approved. It leads the development of Master documents, reviews selection of study facilities and ensures adequate due diligence

processes are in place for the selection of country partners and other service providers. During study conduct, the GST will oversee global recruitment in each country.

- At country level: a Country Study Team (CST) has been established in Vietnam under the coordination of PATH. The CST will be responsible for executing the study. The CST includes core sponsor staff, as well as representatives form NIMPE and MoH. The CST is responsible and accountable for the planning, conducting, and reporting of the country-specific study, in line with the scientific, operational, and quality framework defined by the GST. The CST is responsible for engaging with country stakeholders, including MoH, and ensuring the study design and expected outcomes are aligned with the evidence requirements as defined by the MoH. The CST is responsible for study monitoring and for tracking study recruitment at country level.

13.3 Patient Safety Oversight

13.3.1 Responsibilities

- The safety oversight will be under the responsibility of the sponsor, through the CST. The CST will be responsible for ensuring that prior to study start, all measures are in place to mitigate for the risk of AHA and SAEs. During study conduct the CST will be responsible for making sure that individual patients are properly followed-up by HCPs, and that any suspected or confirmed case of AHA is properly followed and managed (see below). On a regular basis, the CST will evaluate whether new or increased risks to patients and HCPs have aroused and if so, will take appropriate action.
- A Safety Review Team (SRT) will be set up to include the MMV Chief Medical Officer (CMO) as a member. The SRT provides the CST a mechanism to share and consult with the funder (MMV) on safety issues on an ongoing basis. The SRT also provides the MMV CMO an opportunity to evaluate the risk/benefit balance to patients of the study.
- In addition, an Independent Study Oversight Committee (ISOC) will be set up which may include representatives from the MoH as well as public health experts, familiar with the management of vivax patients in Vietnam and experienced in conducting or overseeing epidemiological or clinical studies. The ISOC scope of responsibilities differs from a Data and Safety Management Board (DSMB) in that the ISOC is not responsible for monitoring and safeguarding the safety of individual study participants. This is to fall under the joint responsibility of the study sponsor, the ECs overseeing the study and the national competent authorities. Rather, the ISOC will participate in the general safety assessment and review the data if there is any safety concern regarding the study implementation raised by SRT during the study. The ISOC scope will be further defined in an ISOC charter. However, the ISOC will meet once prior to study start to ensure endorsement of the study plans and meet again at the end of the study. If an ad-hoc meeting is required, the ISOC may recommend that the implementation package be modified, and that additional measures be implemented for the rest of the study.

13.3.2 Patient follow-up

Under routine care, individual patient follow-up is mostly passive and falls under the responsibility of the HCP or dedicated VHW. In the study, although HCPs/VHW will remain responsible for patient follow-up, additional efforts will be made to minimize the number of patients who are Loss-to-Follow-Up (LFU). If a patient does not come back, HCPs will be instructed to attempt to reach the patient for an in-person or remote visit. In addition, the CST will compile patient follow-up rates on a monthly

basis, for each study facility. If follow-up rates are low, additional efforts and resources will be allocated to patient follow-up.

13.3.3 Non-compliance

On a monthly basis, the CST will review a sub-set of endpoints and indicators that are likely to have consequences for patient safety and may warrant action. Monthly dashboards will be generated from the electronic database. In addition, the CST will review routine monitoring visit reports and in particular the indicators that are essential to ensure patients safety.

As the study being conducted under real-world conditions, the study aims to avoid biasing study findings and learnings. Therefore, corrective actions will only be taken by the CST if there is a significant risk to patients. Actions undertaken by the study team (e.g. refresh-training) will be duly documented and included in the study report.

13.3.4 Management and reporting of adverse events

An **Adverse Event of Special Interest** (AESI) is an AE of scientific and medical concern specific to the product for which on-going monitoring and rapid communication is appropriate within the context of a study. These events necessitate complementary examinations in order to characterize and understand them. This term does not imply a causal relationship with the concerned treatment. AESIs in this study are those related to AHA.

Management of AEs will fall under the responsibility of the treating HCP, in line with current practice. In case of AESI (i.e. suspected or confirmed AHA) or any SAE the HCP will follow existing SOPs used in routine practice. The HCP will be instructed to inform the PI or his/her delegate and/or the study team as soon as he/she becomes aware of the event. The PI or his/her delegate will evaluate whether AHA is confirmed, based on the initial information captured by the HCP and any further investigation conducted at the referral hospital.

This study will not systematically collect mild AEs, as it is not aiming at evaluating the safety of an investigational product, but rather a feasibility study to be run under real-world conditions. However, given that TQ is a new drug, moderate, severe and serious AEs will be monitored and reported. For the purposes of this study, AEs graded as moderate or severe or classified as serious as per the definitions below will be systematically collected and reported. These definitions are used by the national PV system. As part of the implementation package, follow-up visits will be conducted where the HCPs will evaluate whether the patient is experiencing any symptoms or signs of AHA. A standardized checklist has been developed to that end which will be included in the CRF.

In addition, at any point in time, AESI occurring during the study will be captured through a dedicated AHA report form. Completion of this form could be triggered by

- the presence of an early sign of AHA at the follow-up visit as reported by the HCP,
- patient reporting such events outside of the study visits (e.g. through phone contact)
- HCPs, community health workers (CHW) or any other health professionals in study HF or referral hospital becoming aware of such an event

The PI and the study team will review the AHA report form to assess accuracy and completeness before it is transmitted to the sponsor. Additional follow-up reports will be completed whenever new information becomes available. Each time new information is available, the PI or his/her delegate will re-evaluate whether the AHA is confirmed or ruled out, prior to transmitting an updated report to the sponsor. Safety data related to AHAs will be reported on a regular basis to the SRT.

All AHA report forms are to be transmitted to the sponsor within 24 hours of occurrence or within 24 hours of the PI becoming aware of the event. Whenever available, anonymized copies of laboratory results and other examinations should be annexed to the AHA report form.

In addition to AHA events, all serious adverse events (SAEs) as well as severe and moderate AEs will be assessed through the follow-up visit and through spontaneous reporting to the HCPs and study team, as per national pharmacovigilance policies. HCPs will be instructed during training to assess and monitor SAEs as well as severe and moderate AEs during the follow-up visit and any other contact with participants according to the following definition.

A serious adverse event (SAE) will be defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

- Requires inpatient hospitalization or prolongation of existing hospitalization, except for routine hospitalization for *Plasmodium vivax* or *falciparum* malarial disease
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

SAE reports will be submitted also to all relevant ethics committees. All AHAs and related SAEs will be reported by PI to NIMPE IRB and PATH. All unrelated SAEs will be reported as required to the relevant ethics committees and PATH within 72 hours of the PI's notification. PATH will share relevant safety reports to GSK as the manufacturer of tafenoquine and MMV as the funder of the study in a regular basis.

In addition, if the PI becomes aware of any SAEs during study conduct, he will also communicate these cases to the sponsor medical representative within 24 hours of him becoming aware of the related SAE and within 72 hours for other SAEs. SAE data collection will rely on routine PV forms. Whenever available, anonymized copies of laboratory results and other examinations should be annexed to the SAE form.

In addition, AESI, life-threatening, and severe and moderate AEs will be reported to the national PV system as applicable. The reporting of these AEs to the national PV system will be monitored throughout the study. Severe and moderate AEs are defined by the national PV system as follows:

- Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated.
- Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated.
- Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

Detailed safety management will be described in a safety assessment plan that will be available before enrolment of the first patient in the study.

Guidance for handling the treatment failure and AHA is also included in the appendix 5.

14 Publication policy

Upon study completion and finalization of the study report the results of the study will be submitted for publication in a peer-reviewed open access journal and posted in a publicly accessible database.

Authorship of any publication will be based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals as defined by the International Committee of Medical Journal Editors (ICMJE).

15 Sex and gender issues

15.1 How sex and gender issues are addressed in the studies

This study is expected to generate knowledge equally applicable to men and women. Data collection will be desegregated by sex which would provide better insights on how to improve access to diagnosis and treatment for malaria for both sexes.

The evidence generated would also inform better patient management. Existing point of care qualitative diagnostics for detecting G6PD deficiency have limited clinical utility when used among women - while males can be either G6PD deficient or not, females have a broad range of G6PD deficiency (Domingo et al., 2019). The intermediate range is not readily identified by qualitative point of care technologies and because of this risk, some countries have restricted access to RC among women (Anderle et al., 2018) .This study aims to generate knowledge in support of expanded access to RC with G6PD testing, which allows for identification of women with intermediate status, and therefore supports equitable use of radical cure and confers the benefits of that treatment to both men and women.

Due to 8-AQ being contraindicated in pregnancy and lactation <6 months post-partum, prior to study start and treatment, it will be ensured there are processes in place to evaluate pregnancy and breastfeeding status, both at baseline and during the study. Relevant training (and/or re-training) of HCP will be provided as needed.

15.2 Sex, gender and recruitment of HCP and patients

The study employs a passive recruitment strategy in HF in addition to active case detection. Both recruitment strategies could in theory result in a less representative sample in terms of sex and gender. In addition, due to the epidemiology of the *P. vivax* vector, more males than females may be infected. Therefore, lower recruitment rates for females could be observed as a result of gender differences in terms of women seeking care more often for their children or male family members rather than themselves because of their status as the primary family caretaker (World Health Organization (WHO) & Roll Back Malaria, 2007). However, the recruitment strategies are well-suited for the purpose of these studies due to their real-world nature.

The study will also include women of child-bearing potential. The benefits of new knowledge acquired on the treatment of *P. vivax* malaria is of high benefit to women given their risk of serious adverse events stemming from the use of RC without screening for G6PD deficiency. In view of these benefits, the studies do not discriminate regarding the recruitment of women when it comes to inclusion and access to research.

15.3 Research findings and reporting

The reporting of research findings will consider sex differences to ensure generalizability of the research findings and their applicability to both women and men as indicated in the SAGER guidelines (Heidari et al., 2016). The studies will stratify the results based on sex and in particular:

- The terms “sex and gender” will be used in such a way as to avoid confusion and will be clearly distinguished.

- The studies are designed in a way to reveal sex-related differences in the results. For instance, data on patient sex is collected to assess the primary and secondary endpoints of the study.
- The final report of the study will include, where relevant, reporting of sex differences.

15.4 Governance of the study

In terms of the governance of the studies at global and country levels, there is a strong female representation at both leadership and mid-level positions across the consortiums, governance bodies as well as at country level.

This balanced representation of women allows for the inclusion of diverse perspectives both on the technical and operational side of the studies. Previous research has proven women's participation in health leadership allows for more gender-responsive programs and policies, more functional health systems and an expanded health agenda(World Health Organization (WHO), 2019).

16 Limitations and problems anticipated

The study acknowledges the competing importance of ensuring safety of study participants, as well as on the other hand, the need to maintain the routine of clinical practice, to ensure applicability of research findings into existing practice and settings as well as relevance to policy uptake. In view of these, interventions by study team in routine practice will be acknowledged and accounted for in future study recommendations to be made.

The study also acknowledges that due to the limited sample size expected in Vietnam, there are concerns about the studies expected statistical power and external validity. Further, the study will make some comparisons regarding endpoints across case-finding strategies but does not expect those comparisons to be statistically significant. One way to mitigate the risk of low samples size will be to organize additional active case detection campaigns and to use enhanced methods for case identification, including microscopy with trained microscopists. Further, the results of this study will be combined with data from other TQ feasibility studies in Brazil, Peru, Ethiopia and Thailand to better understand the safety implications of using TQ as part of routine care. These additional studies will help support the external validity of the data generated in Vietnam. Finally, the low and variable caseloads anticipated in Vietnam are similar to many elimination contexts were NMPCs may be motivated to use G6PD testing with TQ to interrupt transmission and further reduce the malaria burden. Lessons from Vietnam in this study will be useful to inform decisions in other elimination settings.

17 Finance and Insurance

17.1 Funding

The feasibility studies falling under this Master Protocol are funded by Unitaid as part of the grant to MMV and partners to provide equitable access to appropriate *P. vivax* treatment options and reduce the global disease burden by accelerating target country adoption of radical cure tools. They form an essential part of the Partnership for Vivax Elimination (PAVE) initiative led by MMV and PATH which supports endemic countries in achieving their *P. vivax* malaria elimination goals through generating and consolidating evidence on new tools and strategies to increase access to radical cure for *P. vivax* malaria. In addition, the Bill and Melinda Gates Foundation will co-fund this study in Vietnam.

17.2 Insurance

A no-fault insurance has been made available for all participants enrolled in the study to cover all consequences of damages resulting from the research. Subjects who suffer injury as a result of their participation in the study will be entitled to free medical treatment for such injury and to such financial assistance as would compensate them equitably for any resultant impairment, disability or handicap.

1. References

Alam, M. S., Kibria, M. G., Jahan, N., Thriemer, K., Hossain, M. S., Douglas, N. M., Phru, C. S., Khan, W. A., Price, R. N., & Ley, B. (2018). Field evaluation of semi-quantitative point of care diagnostics to measure glucose-6-phosphate dehydrogenase activity. *PLOS ONE*, *13*(11). https://doi.org/10.1371/journal.pone.0206331

Anderle, A., Bancone, G., Domingo, G., Gerth-Guyette, E., Pal, S., & Satyagraha, A. (2018). Point-of-Care Testing for G6PD Deficiency: Opportunities for Screening. *International Journal of Neonatal Screening*, *4*(4). https://doi.org/10.3390/ijns4040034

Baird, J. K., Valecha, N., Duparc, S., White, N. J., & Price, R. N. (2016). Diagnosis and Treatment of *Plasmodium vivax* Malaria. *The American Journal of Tropical Medicine and Hygiene*, *95*(6 Suppl). https://doi.org/10.4269/ajtmh.16-0171

Battle, K. E., Karhunen, M. S., Bhatt, S., Gething, P. W., Howes, R. E., Golding, N., van Boeckel, T. P., Messina, J. P., Shanks, G. D., Smith, D. L., Baird, J. K., & Hay, S. I. (2014). Geographical variation in Plasmodium vivax relapse. *Malaria Journal*, *13*(1). https://doi.org/10.1186/1475-2875-13-144

Chu, C. S., Bancone, G., Kelley, M., Advani, N., Domingo, G. J., Cutiongo-de la Paz, E. M., van der Merwe, N., Cohen, J., & Gerth-Guyette, E. (2020). Optimizing G6PD testing for Plasmodium vivax case management and beyond: why sex, counseling, and community engagement matter. *Wellcome Open Research*, *5*. https://doi.org/10.12688/wellcomeopenres.15700.2

Commons, R. J., Simpson, J. A., Watson, J., White, N. J., & Price, R. N. (2020). Estimating the Proportion of Plasmodium vivax Recurrences Caused by Relapse: A Systematic Review and Meta-Analysis. *The American Journal of Tropical Medicine and Hygiene*, *103*(3). https://doi.org/10.4269/ajtmh.20-0186

Council for International Organizations of Medical Sciences (CIOMS). (2016). *International Ethical Guidelines for Health*-related Research Involving Humans.

Domingo, G. J., Advani, N., Satyagraha, A. W., Sibley, C. H., Rowley, E., Kalnoky, M., Cohen, J., Parker, M., & Kelley, M. (2019). Addressing the gender-knowledge gap in glucose-6-phosphate dehydrogenase deficiency: challenges and opportunities. *International Health*, *11*(1). https://doi.org/10.1093/inthealth/ihy060

Douglas, N. M., Poespoprodjo, J. R., Patriani, D., Malloy, M. J., Kenangalem, E., Sugiarto, P., Simpson, J. A., Soenarto, Y., Anstey, N. M., & Price, R. N. (2017). Unsupervised primaquine for the treatment of Plasmodium vivax malaria relapses in southern Papua: A hospital-based cohort study. *PLOS Medicine*, *14*(8). https://doi.org/10.1371/journal.pmed.1002379

Edwards SJ, Braunholtz DA, Lilford RJ, Stevens AJ. Ethical issues in the design and conduct of cluster randomised controlled trials. BMJ. 1999 May 22;318(7195):1407-9. doi: 10.1136/bmj.318.7195.1407. PMID: 10334756; PMCID: PMC1115783.

Eticha T, Tamire T, Bati T. Performance Evaluation of Malaria Pf/Pv Combo Test Kit at Highly Malaria-Endemic Area, Southern Ethiopia: A Cross-Sectional Study. J Trop Med. 2020 Sep 7;2020:1807608. doi: 10.1155/2020/1807608. PMID: 32963553; PMCID: PMC7492921.

Gerth-Guyette, E., Adissu, W., Brito, M., Garbin, E., Macedo, M., Sharma, A., Das, S., Lacerda, M. V. G., Pereira, D., Talukdar, A., Yilma, D., Pal, S., Zobrist, S., & Domingo, G. J. (2021). Usability of a point-of-care diagnostic to identify glucose-6-phosphate dehydrogenase deficiency: a multi-

country assessment of test label comprehension and results interpretation. *Malaria Journal*, *20*(1). https://doi.org/10.1186/s12936-021-03803-1

Gething, P. W., Elyazar, I. R. F., Moyes, C. L., Smith, D. L., Battle, K. E., Guerra, C. A., Patil, A. P., Tatem, A. J., Howes, R. E., Myers, M. F., George, D. B., Horby, P., Wertheim, H. F. L., Price, R. N., Müeller, I., Baird, J. K., & Hay, S. I. (2012). A Long Neglected World Malaria Map: Plasmodium vivax Endemicity in 2010. *PLoS Neglected Tropical Diseases*, *6*(9). https://doi.org/10.1371/journal.pntd.0001814

Gopichandran V, Luyckx VA, Biller-Andorno N, Fairchild A, Singh J, Tran N, Saxena A, Launois P, Reis A, Maher D, Vahedi M. Developing the ethics of implementation research in health. Implement Sci. 2016 Dec 9;11(1):161. doi: 10.1186/s13012-016-0527-y. PMID: 27938400; PMCID: PMC5148832.

Heidari, S., Babor, T. F., de Castro, P., Tort, S., & Curno, M. (2016). Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use. *Research Integrity and Peer Review*, *1*(1). https://doi.org/10.1186/s41073-016-0007-6

Howes RE, Piel FB, Patil AP, Nyangiri OA, Gething PW, Dewi M, Hogg MM, Battle KE, Padilla CD, Baird JK, Hay SI. G6PD deficiency prevalence and estimates of affected populations in malaria endemic countries: a geostatistical model-based map. PLoS Med. 2012;9(11):e1001339. doi: 10.1371/journal.pmed.1001339. Epub 2012 Nov 13. PMID: 23152723; PMCID: PMC3496665.

Imwong, M., Snounou, G., Pukrittayakamee, S., Tanomsing, N., Kim, J. R., Nandy, A., Guthmann, J., Nosten, F., Carlton, J., Looareesuwan, S., Nair, S., Sudimack, D., Day, N. P. J., Anderson, T. J. C., & White, N. J. (2007). Relapses of *Plasmodium vivax* Infection Usually Result from Activation of Heterologous Hypnozoites. *The Journal of Infectious Diseases*, *195*(7). https://doi.org/10.1086/512241

Ketema T, Bacha K, Getahun K, Portillo HAd, Bassat Q (2021). Plasmodium vivax epidemiology in Ethiopia 2000-2020: A systematic review and meta-analysis. PLoS Negl Trop Dis 15(9): e0009781. https://doi.org/10.1371/journal.pntd.0009781

Lacerda, M. V. G., Llanos-Cuentas, A., Krudsood, S., Lon, C., Saunders, D. L., Mohammed, R., Yilma, D., Batista Pereira, D., Espino, F. E. J., Mia, R. Z., Chuquiyauri, R., Val, F., Casapía, M., Monteiro, W. M., Brito, M. A. M., Costa, M. R. F., Buathong, N., Noedl, H., Diro, E., … Koh, G. C. K. W. (2019). Single-Dose Tafenoquine to Prevent Relapse of *Plasmodium vivax* Malaria. *New England Journal of Medicine*, *380*(3). https://doi.org/10.1056/NEJMoa1710775

Llanos-Cuentas, A., Lacerda, M. v, Rueangweerayut, R., Krudsood, S., Gupta, S. K., Kochar, S. K., Arthur, P., Chuenchom, N., Möhrle, J. J., Duparc, S., Ugwuegbulam, C., Kleim, J.-P., Carter, N., Green, J. A., & Kellam, L. (2014). Tafenoquine plus chloroquine for the treatment and relapse prevention of Plasmodium vivax malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. *The Lancet*, *383*(9922). https://doi.org/10.1016/S0140-6736(13)62568-4

Llanos-Cuentas A, Lacerda MVG, Hien TT, Vélez ID, Namaik-Larp C, Chu CS, Villegas MF, Val F, Monteiro WM, Brito MAM, Costa MRF, Chuquiyauri R, Casapía M, Nguyen CH, Aruachan S, Papwijitsil R, Nosten FH, Bancone G, Angus B, Duparc S, Craig G, Rousell VM, Jones SW, Hardaker E, Clover DD, Kendall L, Mohamed K, Koh GCKW, Wilches VM, Breton JJ, Green JA. Tafenoquine versus Primaquine to Prevent Relapse of Plasmodium vivax Malaria. N Engl J Med. 2019 Jan 17;380(3):229-241. doi: 10.1056/NEJMoa1802537. PMID: 30650326; PMCID: PMC6657225.

Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1): 159-174

Ome-Kaius, M., Kattenberg, J. H., Zaloumis, S., Siba, M., Kiniboro, B., Jally, S., Razook, Z., Mantila, D., Sui, D., Ginny, J., Rosanas-Urgell, A., Karl, S., Obadia, T., Barry, A., Rogerson, S. J., Laman, M., Tisch, D., Felger, I., Kazura, J. W., … Robinson, L. J. (2019). Differential impact of malaria control interventions on P. falciparum and P. vivax infections in young Papua New Guinean children. *BMC Medicine*, *17*(1). https://doi.org/10.1186/s12916-019-1456-9

Recht, J., Ashley, E. A., & White, N. J. (2018). Use of primaquine and glucose-6-phosphate dehydrogenase deficiency testing: Divergent policies and practices in malaria endemic countries. *PLOS Neglected Tropical Diseases*, *12*(4). https://doi.org/10.1371/journal.pntd.0006230

Smith, J. D., Li, D. H., & Rafferty, M. R. (2020). The Implementation Research Logic Model: a method for planning, executing, reporting, and synthesizing implementation projects. *Implementation Science*, *15*(1). https://doi.org/10.1186/s13012-020-01041-8

Takeuchi, R., Lawpoolsri, S., Imwong, M., Kobayashi, J., Kaewkungwal, J., Pukrittayakamee, S., Puangsa-art, S., Thanyavanich, N., Maneeboonyang, W., Day, N. P., & Singhasivanon, P. (2010). Directly-observed therapy (DOT) for the radical 14-day primaquine treatment of Plasmodium vivax malaria on the Thai-Myanmar border. *Malaria Journal*, *9*(1). https://doi.org/10.1186/1475-2875-9-308

Thomson, R., Parr, J. B., Cheng, Q., Chenet, S., Perkins, M., & Cunningham, J. (2020). Prevalence of Plasmodium falciparum lacking histidine-rich proteins 2 and 3: a systematic review. Bulletin of the World Health Organization, 98(8), 558–568F. https://doi.org/10.2471/BLT.20.250621

Weijer *et al* 2012 The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials. PLoS Medicine 2012; 9(11): e1001346 ; Medical Research Council. Cluster randomised trials - Methodological and ethical considerations (2002) MRC UK, London

World Health Organization (WHO). (2019). *Delivered by women, led by men: a gender and equity analysis of the global health and social workforce*. World Health Organization (WHO). https://apps.who.int/iris/handle/10665/311322

World Health Organization (WHO). (2020). *World malaria report 2020: 20 years of global progress and challenge*. World Health Organization. https://www.who.int/publications/i/item/9789240015791

World Health Organization (WHO). (2022). *WHO Guidelines for malaria*. World Health Organization. https://apps.who.int/iris/rest/bitstreams/1332432/retrieve

World Health Organization (WHO), & Roll Back Malaria. (2007). *Gender, Health and Malaria*. https://www.who.int/gender-equity-rights/knowledge/gender-health-malaria.pdf

Zobrist, S., Brito, M., Garbin, E., Monteiro, W. M., Clementino Freitas, S., Macedo, M., Soares Moura, A., Advani, N., Kahn, M., Pal, S., Gerth-Guyette, E., Bansil, P., Domingo, G. J., Pereira, D., & Lacerda, M. V. (2021). Evaluation of a point-of-care diagnostic to identify glucose-6-phosphate dehydrogenase deficiency in Brazil. *PLOS Neglected Tropical Diseases*, *15*(8). https://doi.org/10.1371/journal.pntd.0009649

2. Annexes

Current National Malaria Guidelines of Vietnam

Summary of Product Characteristics (SmPC) for Tafenoquine

SmPC for Primaquine

SmPC for the SD Biosensor STANDARD G6PD Test

Guidance for handling adverse events