Statistical Analysis Plan

WWARN Primaquine Latin America Study Group

# Efficacy, safety, and tolerability of primaquine dose in patients with *Plasmodium vivax* malaria in Latin America: a systematic review and individual patient data meta-analysis

Version 1.0

## WorldWide Antimalarial Resistance Network (WWARN)

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WorldWide Antimalarial Resistance Network (WWARN)
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# 1. Introduction and Rationale

*Plasmodium vivax* is a main cause of human malaria outside of sub-Saharan Africa. In regions where historically *P. vivax* and *Plasmodium falciparum* have co-existed, it is becoming the predominant parasite as malaria control moves towards elimination. Relapsing infections due to dormant liver stages of *P. vivax* are a major cause of transmission, morbidity, and mortality. Currently, radical cure with an 8-aminoquinoline (primaquine or tafenoquine) is the only effective strategy to prevent vivax relapses.

Recent systematic, individual patient data meta-analyses (1, 2) suggest that a total high primaquine dose of 7 mg/kg can reduce the rate of *P. vivax* recurrences by half compared to a total low dose of 3.5 mg/kg, with only an additional slight increase in gastrointestinal symptoms. In addition, patients receiving a daily primaquine dose of up to 0.5 mg/kg with G6PD activity of at least 30% have comparable risks of haemolysis to those not receiving primaquine. However, in different locations, uncertainties remain which regimen is the most effective and safe considering the complex interactions between patient (e.g., prevalence of glucose-6-phosphate dehydrogenase [G6PD] deficiency, impaired cytochrome P450 [CYP] 2D6, immunity to malaria), parasite (e.g., relapse periodicity, strain, drug resistance), and geographical (e.g., access to G6PD testing and quality health care, vector presence) factors. They result in varying background risks and potential benefits. In real-world settings, the optimal regimen may well be context specific.

Vivax malaria is highly prevalent in Latin America. Primaquine remains the sole 8-aminoquinoline recommended in most national guidelines in Latin America to prevent vivax relapses, although Brazil is gradually introducing tafenoquine for some regions. In general, Latin American national guidelines recommend a low-dose regimen (3.5 mg/kg total dose; 0.25 mg/kg/day for 14 days or 0.5 mg/kg/day for 7 days) with no universal G6PD testing for most cases, but a higher dose (7mg/kg total; 0.5mg/kg/day over 14 days) can be used for “known relapses” or treatment failures. This study will focus on the Latin American context to inform national malaria control policy on the optimal course of primaquine that balances risks and benefits.

## *1.2. Aim of the study*

The aim of this study is to assess the effect of primaquine dose and regimen on i) efficacy, ii) tolerability, and iii) safety in patients with *P. vivax* malaria in Latin America.

## *1.3. Eligibility criteria for inclusion in analysis*

### ***1.3.1*** *Essential criteria for inclusion of eligible studies*

- Prospective clinical efficacy studies conducted in Latin America, including randomised trials and prospective cohort studies, of uncomplicated vivax malaria
- A minimum active follow up of 28 days from initial antimalarial treatment (42 days for efficacy analysis)
- Treatment with chloroquine or one of six common artemisinin-based combination therapies (ACT; artemether-lumefantrine, artesunate-mefloquine, artesunate-amodiaquine, dihydroartemisinin-piperaquine, artesunate-sulfadoxine-pyrimethamine, artesunate-pyronaridine)
- At least one treatment arm with daily primaquine given over multiple days and commencing within 28 days of blood schizontocidal treatment
- Study meta-data as described in the WWARN Data Management and Statistical Analysis Plans

(3).

### *1.3.2 Essential data for inclusion in analyses*

- Information on use, timing, and mg/kg dose of primaquine
- Baseline data on patient age, sex, weight
- Asexual parasite density at day 0
- Reporting of parasite presence or absence during follow up*
- Haemoglobin (hb) or haematocrit (hct) measured on day 0 and during follow up#
- Gastrointestinal disturbance (vomiting, anorexia, and/or diarrhoea) during follow up§

### *1.3.3 Desirable data for inclusion in analyses*

- Individual tablet or mg dosing
- Documentation on the supervision of drug administration
- Data on food administration with primaquine
- Qualitative or quantitative assessment of G6PD status
- CYP2D6 genotype/phenotype
- Methaemoglobin measured on day 0 and during follow up
- History of malaria within the past 28 days
- History of fever within the last 24 hours at baseline and during follow up
- Data on vomiting within 1-hour post-administration
- Follow up for 180 days or longer
- Follow up through multiple malaria recurrence events

*Efficacy analysis

#Safety analysis

§Tolerability analysis

### *1.3.4 Exclusion criteria for all analyses*

- Pregnancy or lactation
- Severe malaria
- Receiving adjunctive antimalarial treatments after the initial schizontocidal treatment

## *1.4. Data Pooling*

Embase, Medline, Web of Science, Scopus, and the Cochrane Library will be systematically searched based on an existing living systematic review (4); to identify prospective, clinical efficacy studies of acute, uncomplicated vivax malaria published between 1 January 2000 and 26 July 2024, inclusive, in any language with a minimum active follow-up of 28 days. Relevant data from unpublished studies will be obtained where possible. Studies that fulfil the study criteria will be targeted through direct email to the corresponding author and/or principal investigator. Once data are uploaded into the WWARN repository, they will be curated and standardised using the WWARN Data Management and Statistical Analysis Plans (3) for clinical data and pooled into a single database of quality-assured individual patient data.

# 2. Outline of Statistical Analysis

## *2.1 Specific objectives of the study*

1. To investigate the effect of total primaquine mg/kg dose and regimen duration on the risk of *P. vivax* recurrence
2. To investigate the effect of daily primaquine mg/kg dose on drug tolerability
3. To investigate the effect of daily primaquine mg/kg dose on haematological adverse effects

## *2.2 Study endpoints*

Primary:

- Efficacy: Time to first *P. vivax* recurrence from the day after the last primaquine dose to day 150 after the last primaquine dose
- Safety: 25% drop in haemoglobin to below 7 g/dL between baseline and days 1–14 after starting primaquine
- Tolerability: A composite endpoint including any of the following symptoms of gastro-intestinal disturbance on days 5–7 after starting primaquine: vomiting, anorexia, diarrhoea

Secondary Efficacy Endpoints:

- Time to first *P. vivax* recurrence from the day after the last primaquine dose to day 90 after the last primaquine dose
- Time to first symptomatic *P. vivax* recurrence from the day after the last primaquine dose to day 150 after the last primaquine dose

Secondary Tolerability Endpoints:

- Presence of a composite endpoint of any of the following symptoms of gastro-intestinal disturbance on days 1–2 after starting primaquine: vomiting, anorexia, diarrhoea
- Vomiting within 1 hour of primaquine dosing at i) days 0-2 and ii) days 3-14 after starting primaquine

Secondary Safety Endpoints:

- Maximum absolute reduction in haemoglobin between baseline and days 2–3 after starting primaquine
- Presence of any of the following: haemoglobin fall below 5 g/dL or haemoglobin fall >5 g/dL from baseline between days 1–14 after starting primaquine or renal failure needing dialysis, blood transfusion or death between days 1–28 after starting primaquine.
- Development of mild, moderate, or severe anaemia by days 2–3 after starting primaquine (categories are defined in the next section)

## *2.3 Definitions of Endpoints and Time Zero*

*Timing*

Day 0 is defined as the day of initial treatment with a schizontocidal antimalarial.

Day after last primaquine dose is defined as the day after the expected completion of the primaquine regimen. In treatment arms where primaquine was not administered, this day will be the equivalent day to the day after the last primaquine dose in the concurrent primaquine arm of that respective study. If primaquine was given in two treatment arms in the same study over different durations, the day after last primaquine dose in a treatment arm without primaquine of the same study will be considered as the latter of the two respective days.

*Primary*

"*P. vivax* recurrence before day X" is defined as any episode of *P. vivax* parasitaemia, irrespective of symptoms, between the day after last primaquine dose and day X.

*Secondary*

"Symptomatic *P. vivax* recurrence" will be defined as any episode of *P. vivax* parasitaemia in patients with a temperature ≥37.5°C or a recent history of fever.

Anaemia will be defined as:

- Mild (Hb ≥8 g/dL and <11 g/dl),
- Moderate (Hb ≥5 g/dL and Hb <8g/dl)
- Severe (Hb <5g/dL)

## *2.4 Study and patient characteristics*

The following baseline characteristics will be examined.

Site: regional relapse periodicity, transmission intensity, geographical location

Patient: age, sex, weight, history of malaria in the last 28 days, history of fever in the last 24 hours, fever (≥37.5°C axillary)

Drug: schizontocidal treatment, primaquine use (start day, duration, mg/kg dose), association with food intake, supervision of drug administration (full or partial), early (within 1 hour) vomiting post-drug administration

Laboratory: parasite density, haemoglobin concentration, haematocrit, G6PD status, CYP2D6 status

Children will be considered as aged <15 years with childhood stratified into patients <5 years and those 5 to <15 years.

Schizontocidal treatment will be classified as supervised if all doses were directly observed, partially supervised if at least the morning doses of a twice daily regimen was observed, and not-supervised if fewer doses were observed.

Primaquine treatment supervision will be classified as:

- Supervised if all doses were directly observed

- Partially supervised if >1 dose were observed
- Unsupervised if 0 or 1 dose were observed.

In studies with haematocrit measured instead of haemoglobin, haematocrit will be converted to haemoglobin using the following formula (7):

$$haemoglobin = \frac{haematocrit \times 5.62}{2.60}.$$

For each study, locations of study sites will be recorded. Each location will be categorised into low, moderate, or high transmission settings based on the malaria endemicity estimates obtained for subnational regions and year from the Malaria Atlas Project (8).

G6PD deficiency will be classified as deficient (<30% activity or a positive qualitative test, e.g., by FST) or normal (≥30% activity or a negative qualitative test). A second categorisation will be explored to assess patients with intermediate deficiency (≥30% to <70% activity).

CYP2D6 status will be classified by expected phenotype using the activity score system (10, 11) to estimate phenotype from genotype. The activity score assigns values of 0 to 2 to the *CYP2D6* alleles genotyped in the patient as follows: zero, no-function alleles (e.g., **4*, **4xN*, **5*); 0.25, substantially decreased-function (**10*); 0.5, decreased-function (**9, *17, *29, *41*); 1, normal-function (**1, *2, *39*) and 2, increased function (**1xN, *2xN*). The activity score of diplotypes results from the sum of the assigned value to each allele. Patients with an activity score of 0 are designated as poor metabolisers. Patients with an activity score ∈ {0.25, 0.5, 0.75, 1} are designated as intermediate metabolisers. Patients with AS >2.25 are designated as ultrarapid metabolisers, respectively. Patients with an activity score ∈ {1.25, 1.5, 2, 2.25} are designated as normal metabolisers (12).

Schizontocidal elimination half-life will be defined as i) short (<1 day), ii) intermediate (1 to 7 days), and long (>7 days) (13).

## *2.5 Exposures of interest*

The doses of treatment received (i.e. primaquine, chloroquine, ACT) will be calculated from the number of daily tablets administered to each patient. If the daily tablet counts are not available, doses will be back-calculated using the dosing scheme available from study protocols. For each component, a total dose per weight will be calculated for each patient.

Total primaquine dose will be assessed as a categorical variable primarily to enable comparison of low vs. high dose regimens. Additional analyses will be undertaken with primaquine dose as a continuous variable to investigate the impact of small changes in dose. Total primaquine dose categories will be considered very low dose if <2 mg/kg primaquine is given, low dose if 2 to <5 mg/kg is given, and high dose in ≥5 mg/kg is given (14).

Daily PQ mg/kg dose will be defined as low dose if <0.375 mg/kg/day, intermediate dose if ≥0.375 and <0.75 mg/kg/day, and high dose if ≥0.75 mg/kg/day.

Primaquine regimens will be classified as the duration of treatment in days and will be explored in treatment arms with a similar total mg/kg dose. Primaquine regimens of 7- and 14-days will be compared.

## *2.6 Summary of statistical analyses*

### 2.6.1 Description and characteristics of studies

A profile summary of the relevant studies uploaded to the WWARN repository will be presented to highlight potential heterogeneity.

A summary of the relevant studies will be presented, including (but not restricted to) treatment given, follow up duration, study populations, description of location and transmission intensity, timing, and dosing of primaquine administration.

A comparison table of the summary statistics of studies that were targeted but not included will be presented to allow evaluation of inclusion bias related to study selection.

### 2.6.2 Baseline characteristics of patients:

A summary of relevant baseline patient characteristics will be presented for all patients, those not treated with primaquine and those receiving very low, low, or high total dose primaquine. Variables presented will include age and age group, sex, weight, haemoglobin concentration at baseline, asexual parasitaemia at baseline, presence of fever (temperature ≥37.5°C or fever recorded) at baseline, blood schizontocidal treatment, mg/kg total and daily dose and timing of primaquine (i.e., first day of treatment), percentage of primaquine administered with food, and host variants (G6PD status, CYP2D6 status). The distribution of continuous variables will be described using the mean and standard deviation or the median and interquartile range.

### 2.6.3 Baseline efficacy and treatment related analyses

#### Primaquine treatment dosing

A summary of the distribution of mg/kg primaquine dose will be presented. The distributions will be calculated separately for different age groups, blood schizontocidal drugs, dosing strategies (per protocol vs actual dose), and presented in tables (mean (SD)) as well as visualised using box and whisker plots, histograms or scatter plots (e.g. mg/kg dosing vs age or weight).

#### Time to first *P. vivax* recurrence

Time to first recurrent vivax parasitaemia will be used to compute the Kaplan-Meier estimates of risk of *P. vivax* recurrence at day 90, and day 150 after the last primaquine dose for treatment arms with and without primaquine for each study site where there was a minimum of 42 days follow up. Patients who received primaquine will be left censored (origin) at the day after the last primaquine dose was administered. Patients who did not receive primaquine will be left censored at the day after the last day of the expected primaquine regimen in the concurrent primaquine arm in that study. Patients will

be right censored (exit time) at time of recurrent vivax parasitaemia, first non-vivax malaria parasitaemia, lost to follow up, >67 days blood smear gap, last day of study or the day the outcome is being assessed. The linear association of the continuous covariates and the outcome will be assessed using fractional polynomials. The Kaplan-Meier curves stratified by categories of primaquine total dose and no primaquine use will be presented. Subgroup analyses for age group and duration of primaquine regimen will be undertaken when there are sufficient data.

The proportion of patients who had a recurrent vivax parasitaemia before day 90 and between day 90 and 150 after the last primaquine dose, will be presented.

Cox proportional hazards model will be fitted to the time to first recurrence during follow-up (from the day after the last primaquine dose to day 150 after the last dose) with primaquine total dose (mg/kg, categorical and continuous separately), age (years), sex (male, female), and baseline parasite density (parasites per µL blood, on the log scale), with shared frailty for study site. Proportional hazards assumption will be checked. If possible, subgroup analyses will be undertaken for different schizontocidal treatments, duration of primaquine treatment and age groups. Cox regression analyses will be repeated with symptomatic recurrence as the endpoint of interest. Sensitivity analyses will be undertaken in i) patients commencing primaquine before day 7 to assess the time to first recurrence during follow-up between day 7 and day 150 after last dose, ii) patients with first recurrence between day 7 and 180, iii) patients administered chloroquine and/or 14-day primaquine iv) without shared frailty for study site, v) in studies with follow up for 180 days or more, vi) in patients where the actual dose of primaquine was available, and vii) by removal of one study site at a time.

### 2.6.4 Tolerability related analyses

#### Risk of gastrointestinal intolerance following primaquine

The percentage of patients with each of vomiting, anorexia, or diarrhoea reported on days 5–7 after starting primaquine will be presented in a tabular format. A composite endpoint including any of vomiting, diarrhoea and anorexia on days 5–7 after starting primaquine will also be presented. Results will be presented by daily primaquine mg/kg dose (no primaquine, low dose, intermediate dose, and high dose).

In view of the confounding effect of malaria and coadministration of blood schizontocidal drugs, the composite endpoint will be repeated to identify the presence of any gastrointestinal symptoms in patients on day 0 and on days 1–2 and compared to the percentages on days 5–7 among those who did not receive primaquine or started primaquine on day 0.

A multivariable logistic regression analysis will be undertaken to determine the effect of daily mg/kg primaquine dose (categorised as no primaquine, low dose, intermediate dose, and high dose) on the odds of fulfilling criteria for the composite gastrointestinal endpoint on days 5–7 after starting primaquine. The linear association of the continuous covariates and the outcome will be assessed using fractional polynomials. A separate sensitivity analysis will be undertaken to establish the robustness of this result against results from composite scores generated from individuals asked about all three symptoms versus any two symptoms versus one symptom. Separate analyses will be undertaken for

each gastrointestinal symptom. The effect of daily primaquine dose (mg/kg) will be controlled for age (years), sex (male, female), baseline parasite density (parasites per µL blood, on the log scale), and study site.

The multivariable logistic regression analysis will be repeated for the composite gastrointestinal endpoint on days 1–2. This analysis will be restricted to patients in a treatment arm without primaquine or starting primaquine on day 0.

### Risk of acute vomiting following primaquine

The percentage of patients vomiting within an hour of primaquine dosing will be presented in a tabular format. Results will be categorised by daily primaquine mg/kg dose (no primaquine, low dose, intermediate dose, and high dose) and the risks presented on days 0 to 2 and days 3 to 14 after starting primaquine.

If data allows, a multivariable logistic regression analysis will be undertaken to determine the effect of daily mg/kg primaquine dose (both as a continuous variable and a categorical variable categorised as no primaquine, low dose, intermediate dose and high dose) on the odds of vomiting within an hour of primaquine dosing on any day between 0 and 14 after starting primaquine.

## 2.6.5 Haematological safety related analyses:

### Risk of additional adverse events

The percentage of patients with each of the following will be presented, categorised by daily primaquine mg/kg dose (no primaquine, low dose, intermediate dose and high dose) in patients with G6PD activity ≥30%:

- ≥25% drop in haemoglobin to below 7 g/dL between initial primaquine treatment and days 1–14 after starting primaquine
- Composite outcome of:
    - Blood transfusion day 1–28 after starting primaquine
    - >5g/dL drop in haemoglobin between initial primaquine treatment and days 1–14 after starting primaquine
    - Haemoglobin fall below 5 g/dL between days 1–14 after starting primaquine
    - Renal failure needing dialysis between days 1–28 after starting primaquine
    - Death between days 1–28 after starting primaquine
- Development of mild, moderate, or severe anaemia by days 2–3 after starting primaquine
- Maximum change in haemoglobin between initial primaquine treatment and the minimum measurement on days 2–3 after starting primaquine

A sensitivity analysis will be undertaken to assess the effect of primaquine regimen timing on haematological safety by comparing the absolute reduction of haemoglobin for patients on day 2-3 after starting primaquine in with those who started primaquine on day 0 with those who started after day 7.

Subgroup analyses will be undertaken to compare G6PD intermediate (≥30 and <70%) versus G6PD normal (≥70%) versus G6PD unknown patients if feasible.

Multivariable logistic regression analyses will be undertaken to determine the effect of daily mg/kg primaquine dose on the haematological safety outcomes above in patients with ≥30% G6PD activity. Covariates to be adjusted in the model include age, sex, baseline parasite density, baseline haemoglobin and study site.

The maximum absolute change in haemoglobin between initial primaquine treatment and days 2–3 after starting primaquine in patients with ≥30% G6PD activity will be calculated and presented visually (histogram and box and whisker plot) by daily primaquine mg/kg dose (no primaquine, low dose, intermediate dose and high dose). Subgroup analysis will be undertaken to compare G6PD intermediate (≥30% and <70%) versus G6PD normal (≥70%) versus G6PD unknown patients if possible.

Multivariable linear regression analyses will be undertaken to determine the effect of daily mg/kg primaquine dose (categorised as no primaquine, low dose, intermediate dose, and high dose) on haemoglobin at days 2–3 after initial primaquine treatment in patients with ≥30% G6PD activity. The effect of primaquine dose will be adjusted for age, sex, baseline parasite density, baseline haemoglobin and study site. Subgroup analysis will be undertaken to compare G6PD intermediate (≥30% and <70%) versus G6PD normal (≥70%) versus G6PD unknown patients if possible.

Multivariable logistic regression analyses will be undertaken to determine the effect of daily mg/kg primaquine dose (categorised as no primaquine, low dose, intermediate dose, and high dose) on the risk of developing anaemia at days 2–3 initial primaquine treatment in patients with ≥30% G6PD activity. The effect of primaquine dose will be adjusted for age, sex, baseline parasite density, baseline haemoglobin and study site. The linear association of the continuous covariates and the outcome will be assessed using fractional polynomials. Subgroup analysis will be undertaken to compare G6PD intermediate (≥30% and <70%) versus G6PD normal (≥70%) versus G6PD unknown patients if possible.

### 2.6.6 Risk of bias relating to individual studies

Potential bias relating to individual studies will be assessed using the ROB2 tool (15) for randomised controlled trials and Joanne Briggs Institute Case Series Tool for single arm studies.

## 3. PRISMA Statement

The analysis will adhere to the PRISMA-IPD guidelines for reporting systematic reviews and meta-analyses of individual patient data (16).

## 4. Tools

All statistical analyses and data visualisation will be carried out using Stata and R. However, when equivalent statistical methods are applied in a different statistical software package, changing the use of statistical software will not require amendment of this SAP.

## 5. Study Group Governance, Management, Coordination and Publication Policy

The Primaquine Latin America Study Group comprises participating investigators who contribute relevant data sets to the pooled analysis. Data sets will remain the property of the investigator and will not be shared without their consent. Dr Andre Siqueira, Prof Marcus Lacerda, Dr Anielle Pina, Dr Megha Rajasekhar, Ms Kathy Nguyen, Prof Ric Price and A/Prof Rob Commons will oversee the statistical analyses. Participating investigators will be recognised in publication as contributors. A Writing Committee will coordinate activities including data analysis and drafting of publications and reports for complete group review. The Writing Committee will comprise a group of interested investigators undertaking the data analysis and preparation of the manuscript. Authors will be recognised according to the ICMJE guidelines and the WWARN publication policy (17).

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