Malaria Elimination Toolkit

Primaquine Roll Out Monitoring Pharmacovigilance Tool (PROMPT)

Malaria Elimination Initiative

UCSF

University of California San Francisco

The Malaria Elimination Initiative is a project of the Global Health Group at UCSF Global Health Sciences.

shrinkingthemalariamap.org

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About the Malaria Elimination Toolkit

The Malaria Elimination Toolkit, developed by the Malaria Elimination Initiative (MEI) at the UCSF Global Health Group, provides national malaria programs and implementing partners with evidence-based, user-friendly tools to strengthen malaria elimination efforts worldwide. The toolkit offers approaches that aim to address the challenges confronting national malaria control programs in low-transmission settings. The MEI has built the toolkit around key areas that enable successful malaria elimination and prevention of reintroduction: advocacy, financing, regional collaboration, surveillance and response, and vector control. By supplementing global malaria policy and guidance, these tools aim to accelerate efforts in the countries that are paving the way for malaria eradication.

The key area(s) to which this particular tool is related is highlighted below. The MEI requests that national malaria programs and implementing partners contact us when using any of the tools in the Malaria Elimination Toolkit. Support in implementing the tool may also be available. Please contact Amanda Chung (amanda.chung@ucsf.edu).

Background

For countries aiming to eliminate malaria, the interruption of transmission of the malaria parasite—*Plasmodium falciparum* or *Plasmodium vivax*—is the ultimate goal. However, the most common treatments for *P. falciparum* malaria—artemisinin derivatives—do not target the parasite's mature gametocytes stage that leads to the infection of and onward transmission by mosquitos. Primaquine is the only drug approved by the World Health Organization (WHO) that effectively destroys mature *P. falciparum* gametocytes and prevents onward transmission.

Since 2012, the WHO has recommended single low-dose primaquine (SLD PQ), given in conjunction with an artemisinin-based combination therapy (ACT), to prevent onward transmission of *P. falciparum* malaria. Despite recommendations from WHO to use low-dose primaquine, few countries include the drug in their national malaria treatment policies. This is primarily because countries remain concerned about the risks of hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, an enzyme deficiency that is common in people living in malaria-endemic settings.

Until recently, G6PD testing required laboratory infrastructure that is often not available in field settings. Now there are two commercially available point-of-care tests, although the costs and feasibility of their widespread use is not yet known. Malaria programs report that if they were capable of easily testing for G6PD deficiency, they would use primaquine to treat malaria cases.

While primaquine may cause hemolytic side effects in individuals who have G6PD deficiency, the potential for hemolysis depends on the dose of primaquine used. The current recommended dose of 0.25mg/kg is low enough to mitigate the risk of hemolytic side effects in individuals who have G6PD deficiency. This low dose also enables treatment without requiring G6PD testing.

Although research shows a low risk of hemolysis following 0.25 mg/kg of SLD PQ treatment, safety concerns among national malaria control programs persist. To address these concerns, the MEI developed the **Primaquine Roll Out Monitoring Pharmacovigilance Tool (PROMPT)** to support the roll out of SLD PQ in malaria-eliminating countries and to support national malaria control programs in rapidly detecting and treating hemolytic adverse events, should they arise after SLD PQ use. Anonymized data from PROMPT not only helps the country collecting data to understand the level of risk, but also can be combined with data from other countries to strengthen global research about adverse events that can inform new mitigation strategies.

What is the Primaquine Roll Out Monitoring Pharmacovigilance Tool (PROMPT)?

PROMPT is an active pharmacovigilance surveillance data collection tool to monitor the safety of WHO-recommended single low-dose (0.25 mg/kg) primaquine (SLD PQ) for the treatment of *P. falciparum* malaria.

PROMPT supports the roll out of SLD PQ in malaria-eliminating countries by providing national malaria control programs and healthcare providers with the methods to track and respond to hematologic response to SLD PQ and to generate evidence on the safety of SLD PQ in treating *P. falciparum* malaria.

Who Is this Tool for?

PROMPT provides a tool to healthcare providers to treat *P. falciparum* malaria with SLD PQ and track related adverse events among patients. PROMPT also provides data to national malaria control programs to improve the roll-out of SLD PQ to treat *P. falciparum* malaria and track adverse events across multiple health facilities.

Where Has this Tool Been Used?

A PROMPT pilot study took place in Swaziland from March 2014–April 2015. PROMPT was used in two hospitals that reported the most malaria patients in the country, and data was collected on 100 patients. The data collected enabled malaria researchers to examine the safety of SLD PQ prior to national roll out of SLD PQ. Overall, the pilot demonstrated that SLD PQ was safe in the population tested.

Empowered by the evidence and results from the PROMPT pilot study, Swaziland's National Malaria Control Program adopted the WHO recommendation as national policy. SLD PQ is now available at clinics, health centers, and referral hospitals across the nation. The adoption and roll out of SLD PQ will contribute to a reduction in malaria transmission and will accelerate the country's path to malaria elimination.

How is PROMPT used?

PROMPT is used by healthcare providers to monitor the potential side effects of SLD PQ after administering the treatment. National malaria control programs also benefit from collecting and aggregating this data to monitor the overall risk and determine risk mitigation strategies of SLD PQ. PROMPT should be used in settings that are rolling out SLD PQ and that need to enhance the monitoring of adverse events.

PROMPT is step-by-step tool over eight-days during which an individual is treated for uncomplicated *P. falciparum* malaria and monitored for any adverse events. **PROMPT is comprised of four parts:**

1. **PROMPT Checklist for Day 0 and Day 7**
   Reminds healthcare providers of the key steps in PROMPT. The checklist can also be printed as a poster for the facility. The PROMPT Checklist is included in this document.
2. **PROMPT Patient Data Collection Form**
   Supports healthcare providers in tracking possible adverse hemolytic events in patients following SLD PQ treatment. The PROMPT Patient Data Collection Form is included in this document.
3. **PROMPT Patient Information Card**
   Given to patients by healthcare providers detailing possible signs of hemolytic adverse events associated with SLD PQ. The PROMPT Patient Information Card is included in this document.
4. **PROMPT Database**
   A Microsoft Excel reporting template that collects all data from patient forms at the health facility level. This database can be sent to the national malaria control program to strengthen risk monitoring at the national-level. The PROMPT Database is a separate Microsoft Excel file and can be found on the Tools section of the MEI's website: shrinkingthemalariamap.org.

Instructions for Healthcare Providers

- Once the national malaria control program has decided to treat confirmed, uncomplicated *P. falciparum* cases with SLD PQ, the program can distribute PROMPT to healthcare providers to collect data on adverse events and provide information to their patients on the signs of hemolytic adverse events.
- **Day 0**: During the patient's first visit (Day 0) when SLD PQ and ACT is administered to treat uncomplicated *P. falciparum*, the healthcare provider should complete the Day 0 section of the PROMPT Patient Data Collection Form to record baseline information and provide the patient with the PROMPT Patient Information Card. This information card will empower the patient to monitor symptoms of possible adverse hemolytic events between treatment with SLD PQ on Day 0 and when he/she returns to the health facility for a follow-up on Day 7.
- **Day 7**: The patient must return for a follow-up visit on Day 7 during which the healthcare provider should perform a repeat blood test to compare hemoglobin levels to the baseline recorded on Day 0. A urine sample should be taken to check for hemolysis.
  In addition to returning on Day 7, the patient can return for follow-up at any time up to 4 weeks after primaquine administration to receive hemoglobin testing and a urine sample to check for hemolysis.
- After the patient's visit, the healthcare provider should enter patient data from the PROMPT Patient Data Collection Form (Day 0 and Day 7) into the Microsoft Excel PROMPT Database. The database aggregates information on whether hemolytic events are seen among patients. Healthcare providers should send the PROMPT Database and/or results of the analysis to national malaria control programs every 3–6 months. The database supports the national malaria control program in monitoring adverse events from multiple facilities.

Instructions for National Malaria Control Programs

- During the roll out of SLD PQ, the national malaria control program should conduct training for healthcare providers on 1) how to use the PROMPT Patient Data Collection Form, 2) what to tell the patient when they give them the PROMPT Patient Information Card and 3) how to enter patient data in the PROMPT Database.
- The PROMPT Checklist for Day 0 and Day 7 may be printed for healthcare providers to put on the walls of their clinic. A poster may assist healthcare providers to check for signs of hemolysis and can educate patients on signs of possible hemolytic events.
- After PROMPT is distributed to healthcare providers, the national malaria control program should request health facilities to send the data recorded in the database every 3–6 months.
- In Swaziland, the national malaria control program used a Samsung T211 Galaxy tablet to track PROMPT data across multiple health facilities in real time. If the Samsung Galaxy tablet is linked via the Internet to a cloud server, health facility-level data can be synced with a central database which can help providers and programs respond to potential hemolytic events rapidly.
- National malaria control programs can determine the risk of serious hemolysis from their data by following the instructions in the Microsoft Excel PROMPT Database.
- To contribute to a global understanding of SLD PQ use and possible adverse events, national malaria control programs are encouraged to share anonymized data with the World Wide Antimalarial Resistance Network (WWARN) (wwarn.org). This network combines data across countries to strengthen research and knowledge about SLD PQ use and risks of adverse events globally. To share data with WWARN, please contact Ingrid Chen (ingrid.chen@ucsf.edu).
- The MEI requests that national malaria programs contact us when using any of the tools in the Malaria Elimination Toolkit. Support in implementing the tool may also be available. Please contact Amanda Chung (amanda.chung@ucsf.edu).

The **Malaria Elimination Initiative (MEI)** at the University of California San Francisco (UCSF) Global Health Group believes a malaria-free world is possible within a generation. As a forward-thinking partner to malaria-eliminating countries and regions, the MEI generates evidence, develops new tools and approaches, disseminates experiences, and builds consensus to shrink the malaria map. With support from the MEI's highly-skilled team, countries around the world are actively working to eliminate malaria—a goal that nearly 30 countries will achieve by 2020.

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PROMPT Checklist for Day 0 and Day 7

Please follow the steps for the initial patient visit on Day 0 (below) and follow up visit on Day 7 (next page):

Checklist for Day 0: Baseline

❑ Step 1

Determine if the patient is eligible to be treated with SLD PQ for confirmed, uncomplicated *P. falciparum* malaria per WHO guidelines.

The following groups of people **should not** receive SLD PQ:

- pregnant women
- women breastfeeding for 6 months or less
- children under 6 months old

❑ Step 2

Refer to the dosage chart and choose the appropriate dose based on the patient's weight. SLD PQ should be given with ACT, together with food.

Weight (kg)	Number of tablets (7.5 mg)	Dose (mg)
10-15	0.5	3.75
16-30	1	7.5
31-45	1.5	11.25
>45	2	15

❑ Step 3

Perform finger prick to evaluate patient's hemoglobin levels.

❑ Step 4

Record patient's information in the PROMPT Patient Data Collection Form (as well as in the patient's medical record and in the health facility patient registry).

❑ Step 5

Schedule patient for a follow up visit in 7 days.

❑ Step 6

Provide patient with the PROMPT Patient Information Card and explain it to the patient.

Checklist for Follow-up Visit (Day 7 or up to four weeks after treatment)

❑ Step 1

Perform finger prick to evaluate hemoglobin levels.

❑ Step 2

Compare hemoglobin at Day 7 to Day 0 using the algorithm below.

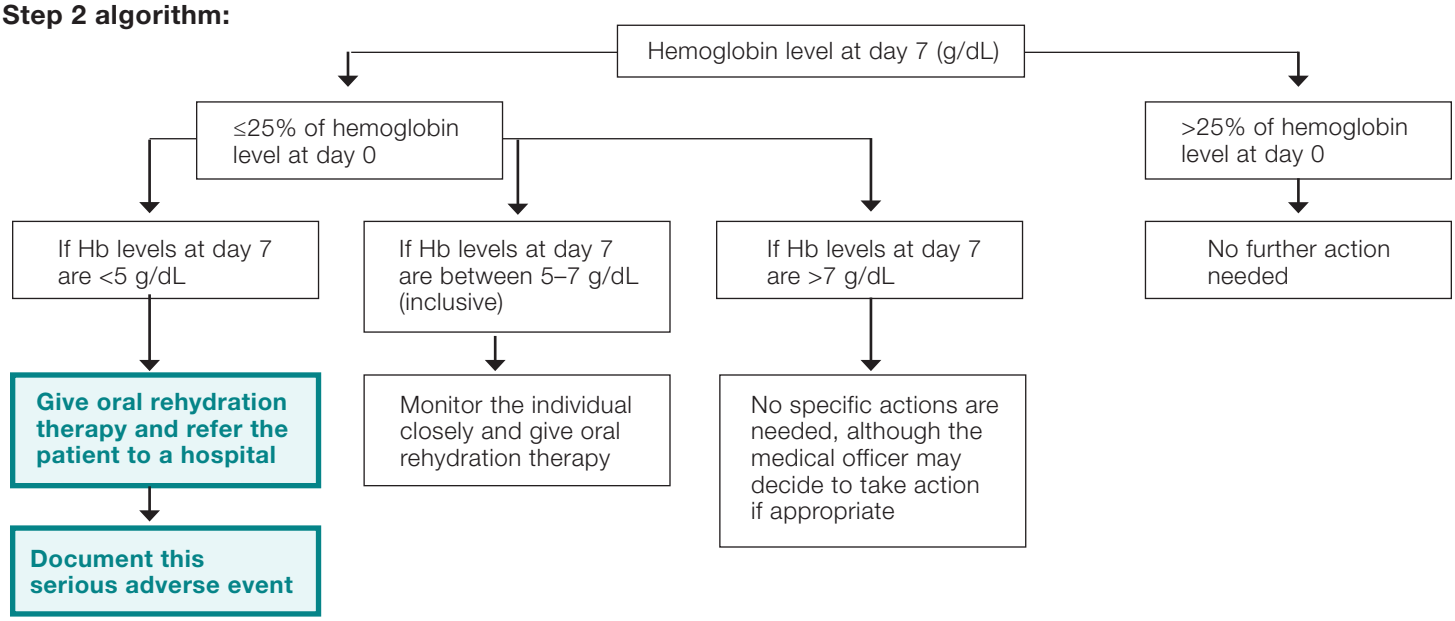
❑ Step 3

Take a urine sample in a clear container.

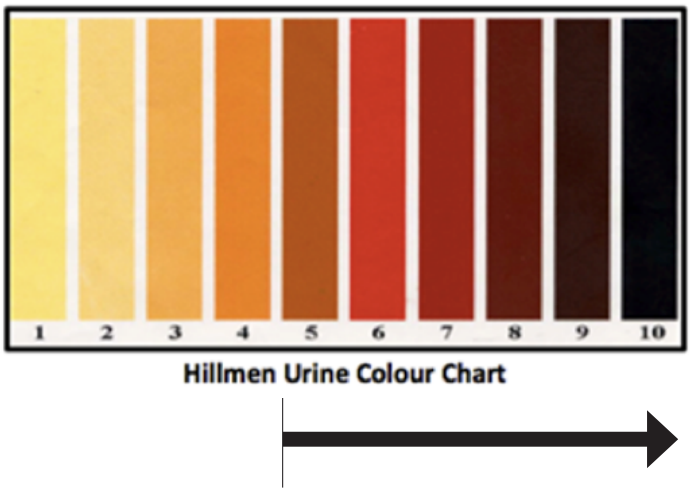
❑ Step 4

Hold the container against a piece of white paper with good lighting and evaluate the color using the Hillmen urine color chart.

Step 2 algorithm:



Step 4 Hillmen urine color chart:



If the color of urine is 5 or higher, give the patient oral rehydration therapy and refer him/her to hospital

PROMPT Patient Data Collection Form

Complete this data collection form for all cases of confirmed, uncomplicated *P. falciparum* malaria that have been treated with SLD PQ.

Day 0 (Baseline)

1. Date primaquine given (dd/mm/yy) _ _ / _ _ / _ _

2. Scheduled Day 7 visit: (dd/mm/yy) _ _ / _ _ / _ _

3. Family Name |___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

4. First (Given) Name
|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

5. Age: |__|__| ❑mths ❑yrs 6. Weight: _ _ _. _ kg

7. Mobile No. 1 |___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

8. Antimalarial prescribed (check all given):
❑AL ❑Oral QN ❑Other (specify): _____ ❑Unknown

9. Total primaquine dose prescribed:_____mg

10. Tablet dose given: ❑7.5mg ❑Other (specify): _____ mg/dose

11. # t PQ tablets given:
❑0.5 tablet ❑1 tablet ❑1.5 tablets ❑2 tablets ❑Other (specify): _____

12. G6PD testing conducted?
❑yes ❑no
If yes, result: ❑G6PD-normal ❑G6PD-deficient

Safety Monitoring

13. Date primaquine given (Day 0): Date _ _ / _ _ / _ _ (dd/mm/yy)

14. Day 0 (baseline) hemoglobin taken? ❑Y ❑N
If yes, ❑❑.❑ g/dL

15. Day 0 (baseline) urine color (from Hillmen Colour Chart) ❑❑

Day 7 (Follow-Up)

16. Day 7 (follow-up) Date _ _ / _ _ / _ _ (dd/mm/yy)

17. Day 7 (follow-up) hemoglobin taken? ❑Y ❑N
If yes, ❑❑.❑ g/dL

18. Day 7 (follow-up) urine color (from Hillmen Colour Chart) ❑❑

Repeat if more than one follow-up visit, up to 4 weeks from SLD PQ treatment on Day 0

19. Additional follow-up: Date _ _ / _ _ / _ _ (dd/mm/yy)

20. Follow-up hemoglobin taken? ❑Y ❑N
If yes, ❑❑.❑ g/dL

21. Follow-up urine color (from Hillmen Colour Chart) ❑❑

Swaziland Example: PROMPT Patient Information Card

PROMPT

Primaquine Roll Out Monitoring Tool

Family Name/Sibongo |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

First (Given) Name/Libito |__|__|__|__|__|__|__|__|__|__|__|__|

G6PD test result/Imiphumela yeluhlohlo lwe G6PD: ☐Normal/Lizinga lelifanele ☐Deficient/Lizinga leliphansi

Patient Instructions/ Lokumele kulandzwelwe ngulogulako

You have received treatment for malaria. Please return if you do not improve or notice new problems. Please check the color of your urine (by passing urine into a white or clear container) while taking malaria medications. If you notice dark to very dark urine (reddish-brown) or experience nausea, vomiting, stomach or back pain, please return to the health facility with this card or call the following number: **25053804**. You are scheduled to return to the clinic for a follow up visit in 7 days on __ __ / __ __ / __ __ (dd/mm/yy).

Uniketwe imitsi yekulapha malaleveva. Sicela kutsi ubuye nangabe ungabi ncono noma nawubona timphawu letinsha lebetingekho ekucaleni. Sicela ubonaka umbala wemchamo wakho(loku kungabonakala nawungachamela esikoteleli lesimhlophe noma lesite umbala) nawusachubeka nekunatsa lomutsi. Nangabe kwenteka ubona lomchamo ungumbala lomnyamana kuya kulokumnyama noma ugonyuluka, uhlanta, kubuhlungu sisu noma umgogodla, sicela ubuye emtfolamphilo nalelikhadi leli noma ushayele lemombolo yelucingo lena: **25053804**. Ubhekeke kutsi ubuye emtfolaphilo utocwaningwa emuva kwetinsuku letisikhombisa, mhlaka __ __ / __ __ / __ __ (lusuku/inyanga/umnyaka).

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(logo (s))

Provider Instructions/Lokumele kulandzelwe ngulona lonika lusito

Health Facility Name/Umtfolamphilo: _____
Contact No. for NMCP/Inombolo yelucingo yaka NMCP: **25053804**

Should the patient return with signs or symptoms of commonly reported adverse events associated with primaquine, please complete a patient encounter form. If patient presents to a different health facility from the health facility where original treatment was provided, please contact the National Malaria Control Programne (NMCP).

Nangabe sigulane sibuya siphatsekile sikhomba netimphawu letingabangwa kuniketwa iPrimaquine, gcwalisa imininingwane ledzingekile eformini lelifanele. Nakwentekile lona logulako aye esibhedlela lesinye kunalesi lapho bekatfole khona lomutsi ekucaleni, sicela uchumane ne baka National Malaria Control Programme (NMCP).

If found, please return to NMCP