

Section II: Schedule of Requirements

RFP reference no: RFP/2021/25569

TERMS OF REFERENCE (TOR)

Implementation of Integrated Drug Efficacy Surveillance (IDES) during 2021-2023 for *Plasmodium falciparum* and mixed malaria infections in Cambodia

Background

Cambodia has been implementing Therapeutic Efficacy Studies (TES) for the past few years to assess the efficacy of malaria treatment in the country. These studies have proven to be an important tool in malaria elimination and have informed the modification of treatment guidelines and drug regimens to ensure that treatment available in the country remains efficacious. However, in areas approaching elimination, there are too few cases for TES to continue to operate effectively.

To be able to continue the surveillance activities in Cambodia, several pilots of *Integrated Drug Efficacy Surveillance* (iDES) have been conducted. Following these pilots, the National Centre for Parasitology, Entomology and Malaria Control (CNM) plans to scale up iDES for *P. falciparum* and mixed infections over the course of the next three years, starting in 2021.

Main objective

The key objective of the iDES program is to introduce, scale up and maintain routine surveillance of drug efficacy of Artemisinin Combination Therapies (ACT), the first line treatment for uncomplicated *P. falciparum* and mixed infections, in Cambodia.

Patient follow-up should conform to the following schedule of activities for patients that test positive for *P. falciparum* :

Day	Activities
Day zero At the time of diagnosis and treatment	<ol style="list-style-type: none"> 1. Take two dried blood spots (DBS) for PCR analysis 2. Counsel patients on how to take the ACT according to the manufacturer's instructions and how follow-up is done and how treatment failure will be identified and reported 3. Provide treatment and observe the patient taking the first dose 4. Arrange supervised treatment for day one and two
Day 1 24 hours after the first dose	<ol style="list-style-type: none"> 1. VMW or volunteer to visit the patient to supervise treatment at the same time of day as the first dose
Day 2 42 hours after the first dose	<ol style="list-style-type: none"> 1. VMW or volunteer to visit the patient to supervise treatment at the same time of day as the first dose
Day of suspected treatment failure Or Day 42	<ol style="list-style-type: none"> 1. Take two dried blood spots for PCR analysis 2. Take a blood smear to be read by a trained microscopist within 24 hours to confirm whether the patient has malaria. If so, patients should be treated with second line treatment. If not, the patient should continue to be followed up until day 42.

PCR analysis will be conducted on the dried blood spots collected on day 0 and either the day of suspected treatment failure or day 42 in order to:

- Confirm the diagnosis from the RDT on Day 0
- Analyze molecular markers of drug resistance on Day 0
- Conduct genotyping of malaria parasites on the day of failure to determine if infection is due to reinfection or recrudescence in comparison to Day 0

Dried blood spots collected on Day 0 will be analyzed for markers of partial artemisinin resistance (K13 mutations) and alternative ACT partner drug resistance (Pf Plasmepsin 2/3 for piperazine and Pfmdr1 for mefloquine). In addition, the PCR analyses will be used to calculate overall treatment failure rates for Artesunate-Mefloquine in Cambodia. The resistance and treatment failure data will then be used to inform updates to the national treatment guidelines, where necessary.

Implementation Scope

This IDES shall be implemented nationwide in 21 provinces and 55 endemic ODs and is expected to cover all the Pf/mix cases wherever they occur. Pf/mix caseload has fallen significantly in the last few years with 4,990 Pf/mix cases in 2019, 936 cases in 2020, and only 164 cases through July of 2021.

Implementation Duration

October / November 2021 to December 2023

Primary objective 1: Determine treatment outcomes

All *P. falciparum* and mixed patients should be followed up to determine the outcome of their treatment.

Primary objective 2: Routinely monitor treatment efficacy

Treatment outcome data is to be routinely monitored to determine if the first-line treatment remains effective for clearing parasitemia.

Mandatory requirements

- The bidder shall have a functional malaria microscopy laboratory or else the bidder shall present an MoU identifying a sub contracted microscopy laboratory that they will partner with to implement the service. Note that the subcontracted Laboratory must be legally registered in Cambodia and therefore its registration certificate shall be presented together with the tender.

Minimum requirements of the bidder

- Administrative capacity (i.e. sufficient number of trained staff) to embed within subnational levels across all provinces in Cambodia with *P. falciparum* and mixed infections.

Specific tasks

- Design and implement a program to introduce and scale up iDES to monitor treatment outcomes and drug efficacy for all *P. falciparum* and mixed infections nationwide according to the contractual obligations agreed upon during the contracting process.
- Design and conduct the iDES training to relevant key players. This includes developing training materials, with technical support from CNM.
- Develop a mechanism for collecting, transporting, and analyzing all prepared blood slides and DBS samples from both points of care (e.g., health facilities and community network – VMW & MMW).
- Develop a mechanism of follow-up of all *P. falciparum* and mixed cases nationwide in order to ensure that the cases are captured by the iDES program.

- Integrate iDES results with the national health system, if possible, to ensure timely treatment and follow up.
- Develop mechanism for timely and accurate data collection and collation from all levels of the iDES system (e.g. VMW, HC, hospitals, PCR lab) including patient and sample follow-up.
- Report timely and accurate data to CNM and relevant partners for review and feedback.
- Financial management should be followed under the requirements of the contractor's existing financial management policy that can be auditable by CNM.
- Coordinate with CNM to plan monitoring and evaluation of the quality control.
- Facilitate Quarterly Progress Review Meeting to update progress of activities and findings to CNM and all relevant stakeholders.
- Develop a semi-annual and annual narrative report of iDES implementation, which includes recommendations for CNM.
- The bidder is required to prepare and submit their detailed work plan together with their proposal. Note that this shall be evaluated together with the technical proposal and scores shall be awarded for the plan presented.

Milestones and Deliverables

The following sections detail the expected outputs from the Bidder for each required activity. The assignment shall be divided into four main steps:

1. Design and provide training to key staff and implementing partners
2. Set up a mechanism for sample collection, transport and analysis and follow-up
3. Ongoing activities per schedule, follow-up for Pf. cases. sample analysis, reading and monitoring.
4. Semester and annual reports

Completion Timeframe	Deliverable/Outputs (All deliverables shall be checked and approved by the National Malaria Program)
1st milestone will be completed by June 2022	Design and provide training to 10 provinces which have had Pf/mix cases in 2020 (MIS 2020). These provinces are Kampong Speu, Kampong Thom, Kratie, Monduliri, Preah Sihanouk, Preah Vihear, Pursat, Ratanakiri, Stung Treng and Tbong Khmum.
	Mechanism for sample collection and follow-up has been developed and is being implemented by each of all the 10 provinces mentioned above.
	At least 95% of Pf/mix cases who agree to participate (in those 10 provinces), are completely followed-up with all iDES required activities, including DBS collected on day 42 and PCR analysis completed.
	First semester report completed and submitted for review and approval by CNM
2nd milestone will be completed by December 2022	Scale up the iDES training to the additional 11 endemic provinces. These provinces are Banteay Meanchey, Battambang, Kampong Cham, Kampong Chhnang, Kampot, Kep, Koh Kong, Oddar Meanchey, Pailin, Siem Reap and Takeo.
	Mechanism for sample collection and follow-up are in place for all 21 provinces including the additional 11 provinces
	At least 95% of Pf/mix cases who agree to participate in all 21 provinces including the additional 11 provinces are completely followed-up with all iDES required activities, including DBS collected on day 42 and PCR analysis
	Annual report completed and submitted for review and approval by CNM

3rd milestone and 4th milestone will be completed by June 2023 & December 2023, respectively

1. At least 95% of Pf/mix cases who agree to participate in all 21 provinces (including the additional 11 provinces) are completely followed-up with all iDES required activities, including DBS collected on day 42 and PCR analysis.
2. **Semester report, annual report, and final report** are prepared accordingly and submitted for review and approval by CNM.

In addition to the above milestones, the bidder shall be required to prepare:

1. Monthly progress updates and present these to CNM during the monthly surveillance partners meeting
2. Quarterly reports of the agreed upon indicators are to be submitted to CNM for review and acceptance.

#	Evaluation Indicators to be included in the reports	Type	Numerator	Denominator	Target
1	Number of Pf/mix cases nationwide	Number	N/A	N/A	N/A
2	Number of Pf/mix cases who agree to participate	Number	N/A	N/A	N/A
3	% DBS collected on day zero	Percentage	Number of cases where day zero DBS was collected	Number of Pf/mix cases who agree to participate	100%
4	% of individuals who complete the full course of malaria treatment	Percentage	Number of cases who completed three days of treatment	Number of Pf/mix cases who agree to participate	100%
5	% Cases suspected of treatment failure	Percentage	Number of cases suspected of treatment failure	Number of Pf/mix cases who agree to participate	
6	% Suspected treatment failure where blood smear collected and read by microscopy on day of treatment failure of those who agree to participate	Percentage	Number of cases where blood smear was collected and read by a microscopist on the day of suspected treatment failure	Number of cases suspected of treatment failure	100%
7	% Cases with microscopy-identified treatment failure	Percentage	Number of cases with microscopy-identified treatment failure	Number of Pf/mix cases who agree to participate	< 10%

8	% Cases where DBS was collected on day 42	Percentage	Number of cases where DBS was collected on day 42	Number of Pf/mix cases who agree to participate AND were not suspected of treatment failure	> 80%
9	% Cases who agreed to participate but were lost to follow-up	Percentage	Number of cases lost to follow up	Number of Pf/mix cases who agree to participate	< 20%
10	% Cases where day zero DBS was read by PCR	Percentage	Number of cases where day zero DBS was read by PCR	Number of cases where day zero DBS was collected	> 95%
11	% Cases where day 42 DBS was read by PCR	Percentage	Number of cases where day 42 DBS was read by PCR	Number of cases where day 42 DBS was collected	> 95%
12	% Cases where treatment failure DBS was read by PCR	Percentage	Number of cases where treatment failure DBS was read by PCR	Number of cases suspected of treatment failure	>95%

Annual expectations

An annual review meeting and annual summary document will be expected by the 15th of January of each year, reporting on the previous year's work.

The annual review meeting and annual summary document should contain, at minimum:

- Implementation progress made.
- Review of key indicators and targets, and whether those targets have or have not been met. Indicators should be presented by month for all months of the previous year.
- Challenges encountered.
- General findings, including relevant trends or areas for further analysis.
- Lessons learned and recommendations on improving the system for the coming year.

Payment Schedule (no advanced payment shall be made):

No	Milestones	Schedule of Payment of the total contract sum
1	1st Milestone - will be completed by June 2022 and the first report completed and submitted for review and approval by CNM.	30%
2	2nd Milestone - will be completed by December 2022 and the annual report completed and submitted for review and approval by CNM.	30%
3	3rd Milestone - will be completed by June 2023 and the semester report is prepared accordingly and submitted for review and approval by CNM.	20%
4	4th Milestone - will be completed by December 2023 and the annual and final report are prepared accordingly and submitted for review and approval by CNM.	20%

Note:

- Payment will be made within 30 days after receiving the semester progress report in line with the set milestone for the specific period and upon submission of an original invoice to UNOPS.
- Please note that the report should be approved or accepted by the National Malaria Program (CNM)