

Workshop for the Development of a District-Based (TES) Protocol to Monitor Therapeutic Efficacy of Antimalarials in Lao PDR

23 – 25 March 2010

Vang Thong Hotel

Luang Prabang, Lao PDR

Draft Report

Executive Summary

In the past few years, the significant reduction of malaria prevalence in most countries of the Greater Mekong Sub-region has increased the difficulty to recruit patients to monitor therapeutic efficacy of anti-malarial drugs as per criteria of routine WHO protocol. The workshop contributed to identify the various challenges to be addressed by PIs by using the existing TES protocol pertaining to sentinel site selection, maintenance, patient recruitment, data management and supervision especially in very low prevalence countries such as Lao PDR. Participants were able to draft a revised district-based TES protocol to be piloted in Lao PDR (and further in other GMS countries experiencing similar situation). The estimated budget to implement the revised protocol has yet to be itemized in order to be submitted to WHO by May 2010 and to be performed from October 2010. It was noted that Thailand has been using village-based recruitment in 2 provinces bordering with Cambodia where falciparum cases are almost disappearing. Procedures to internally and externally cross check results from blood smears were reviewed, and country best practices to improve microscopy QC procedures were highlighted. It was agreed to make a better use of the country and regional “WHO accredited list of microscopists” managed by ACTMal in collaboration with WHO in such a way that level 2 microscopists are actually based in the TES sentinel sites to validate slides and level 1 microscopists are used at higher level to cross check all slides from the field. A suggestion was made to pursue efforts made in 2009 to cross check results externally as well by level 1 microscopists from the region facilitated by WHO in all GMS countries.

The PI from Lao PDR presented alternative options to the classic sentinel site approach to carry out TES. The suggestion was to set up 3 sentinel sites (a regional level in the north and in one province in central and southern Lao respectively). The regional sentinel site will encompass 1 or 2 provinces depending on malaria incidence yet to be explored with the involvement of one provincial and 2 district hospitals, several health centers and village volunteers to improve patients’ recruitment in a reasonable period of time. In such a setting, the study duration is extended to 8 months in order to capture 2 peak transmission periods (and to be carried out every 2 years). It was planned to go further with this scenario by exhausting any technical opportunities out of the current protocol (i.e. recruiting patients with lower parasitaemia), by systematically incorporating “WHO accredited microscopists” in selected sentinel sites and by provisioning an adjusted budget estimate to be submitted to WHO as part of the Q4 2010 TES country plan in Lao PDR.

Taking the quasi perfect protocol submitted by the Thai PI to WHO as an example highlighting in red challenging paragraphs and sections which deserve particular attention (e.g. when to be successfully submitted to the Ethical Review Committee (ERC) in Geneva), all other PIs from Cambodia, Myanmar, Thailand and Viet Nam presented their country proposals and estimated budget for 2010. Comments and suggestions were made in plenary by other PIs and facilitators [e.g. Charles Delacollette, Lasse Vestergaard, Rashid Abdur, Dorina Bustos, Tran Cong Dai and Deyer Gopinath]. It was re-emphasized that the complete protocol and informed consent forms [in local and English language] must be part of the protocol when submitted to WHO together with national or institutional ethical clearance.

Background

The Greater Mekong Sub-region (GMS) is well known as the epicenter of *P. falciparum* resistance to antimalarial drugs in the world. It is in this region, comprising Cambodia, China's Yunnan province, Lao PDR, Myanmar, Thailand and Viet Nam that resistance emerged to chloroquine, sulfadoxine-pyrimethamine and mefloquine, before spreading to other parts of the world. All six countries of the Mekong region have introduced artemisinin-based combination therapies (ACTs), which are currently the only effective therapies against multidrug-resistant malaria strains. There is also growing concern of *P. vivax* resistance to chloroquine in the region in such a way that TES with CQ have to be carefully performed in the GMS as well.

In an informal consultation with representatives from all Mekong countries and partners organized by the WHO Mekong Malaria Programme (MMP) in Phuket, Thailand, on 3-5 September 2007¹, the representatives and principal investigators from malaria control programmes of the six countries in the GMS (Cambodia, China, Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam) agreed to use WHO methodologies and guidelines throughout the GMS in 2008 and 2009. Majority of these *in vivo* studies have been financially supported by USAID through WHO-MMP. WHO provided an update on recent protocols and guidelines to monitor therapeutic efficacy of anti-malarial drugs in the world. Participants as representative from National Malaria Programme then developed, budgeted and presented their 2008-9 draft country plans to conduct *in vivo* TES [*P. falciparum* and *P. vivax*] with first-line anti-malarial drugs in 2008 and 2009 in selected sentinel sites. During the last 2 years, TES workshops have been conducted in all countries and country visits have been scheduled in all countries to monitor TES performance as per agreed upon WHO protocol.

In order to take stock of progress made during the last 2 years in the GMS, a TES workshop was held in Mandalay, Union of Myanmar from September 30 to October 2, 2009². Results, accomplishments and challenges were reviewed in plenary and plans made to support future therapeutic efficacy studies to monitor *P. falciparum* and *P. vivax* resistance to anti-malarial drugs in the Greater Mekong Sub-region in 2010 and 2011. 34 sentinel sites have been in operation across the 6 Mekong countries with either 1 or 2 drugs tested against *P. falciparum* or *P. vivax* or both species in 2008 and 2009. All countries have adhered to the standard WHO 28-day or 42-day therapeutic efficacy protocol and have used the WHO recommended Excel programme for data management and reporting.

¹ WHO South-East Asia Region and Western Pacific Region: Monitoring Resistance of *P. falciparum* and *P. vivax* to Antimalarial Drugs in the Greater Mekong Sub-region, Phuket, Thailand, 3-5 September 2007, SEA-MAL-250.

² Workshop to review and plan therapeutic efficacy studies to monitor *P. falciparum* and *P. vivax* resistance to anti-malarial drugs in the Greater Mekong Sub-region Mandalay, Union of Myanmar September 30 - October 2, 2009 – draft report available on the URL: http://www.whothailand.org/EN/Section3/Section113_269.htm

The sample size was calculated according to malaria prevalence and expected rates of failure in the selected sites with an average sample size of at least 50 patients per site. However, this sample was difficult to reach in some sentinel sites due to very low malaria transmission reached as the result of aggressive control measures.

The following observations were highlighted specifically to Lao PDR:

- The classical WHO TES methodology and required sample size could not be achieved in light of the drastic decline of confirmed malaria cases noted in Lao PDR [especially in its Northern part] and the recommended duration of the monitoring period [3 to 6 months during one transmission period]
- Despite active case detection (which is labor intensive) of positive patients in target villages and screening of all fever cases in the hospitals in the 3 sites, very few patients were recruited in the study from June to Sep 2009.
- Current level of reported treatment failure rate with AL is still very low (<5%) in Lao PDR. Current recommended practice as per WHO protocol is to test the same [first line] drug every 2 years. One suggestion made by experts during the meeting was to refine the current technical protocol in 2010 and plan a reoriented TES district-based approach maximizing or exhausting any technical opportunities as per existing protocol.
- Skilled human resources available at site (provincial, district staff and microscopists) are limited with competition between priority activities outside the TES agenda

Objectives of the workshop

At the end of this 3-day workshop, the participants would have:

- 1) Identified the various challenges in the existing protocols pertaining to sentinel site selection, maintenance, patient recruitment, data management and supervision in Lao PDR and other GMS countries;
- 2) Developed a revised district based TES protocol primarily to be used and assessed in Lao PDR;
- 3) Drafted a budget estimate based on new protocol requirements to be submitted to WHO during the 2d quarter of 2010;
- 4) Considered the use of the revised protocol in other suitable GMS countries;
- 5) Fine tuned procedures to internally and externally cross check results from blood smears;
- 6) TA is identified including country visits to support the above

Participants

All country PIs and WHO country malaria officers were present except China (the PI cannot travel due to last minute passport problems). List of participants is in annex 2.

Introduction to the Workshop

The workshop started at 9am, with welcome remarks from Dr Charles Delacollette (CD) on behalf of WPRO and SEARO and the WR Lao PDR. A modified agenda was presented (Annex 1) by CD.

The objectives of the workshop were further explained with focus on 1) developing the district-based therapeutic efficacy study (TES) in countries with very low transmission such as Lao PDR, with updated budget estimate to support the modified protocol 2) finalizing country therapeutic efficacy study proposals and budget estimates per country to be performed in 2010.

Appointment of Chairperson and rapporteur

Prof Samlane Phompida accepted to chair the workshop.

Dr Dorina Bustos, WHO Senior Technical Adviser, worked as facilitator and rapporteur.

Dr Lasse Vestergaard (WHO CLO Vanuatu) was tasked to facilitate separate technical meetings with Lao TES staff to initiate / draft the revised TES protocol.

PROCEEDINGS

DAY 1 - March 23, 2010

Presentations

(1) Technical challenges and options to perform *in vivo* TES in Lao PDR

Dr Viengxay Vanisaveth

Background information was presented on falciparum and vivax cases trends in Laos from 2000 and the use of microscopy and RDT for malaria diagnosis. There is more reliance on the mono Pf RDT especially in villages hence vivax cases may be seriously under-reported. Results of TES in 2001-2005 in 4 sentinel sites showed >95% efficacy of AL and 100% for A+M. In recent years, however, as the direct result of control measures, malaria cases have drastically declined increasing the difficulty to enrol sufficient patients during the short period of time assigned for the study: all sentinel sites in 2009 could not reach the required sample size. Patient recruitment problems and challenges were presented in the 3 sentinel sites (namely Luang Namtha, Khammoune and Attapeu).

Two options were raised to enhance recruitment:

- (1) Have regional sites for the north, central and southern parts of the country. There can be a total of 8 catchment centers per regional site: 2 provincial hospitals, 4 district hospitals and 2 health centers.
- (2) The second option is to do the TES on rotation basis per sentinel province.

It was planned to review and discuss these options through separate sessions with the Laos TES group facilitated by Dr Lasse Vestergaard later in the day. Group outputs were presented in plenary on Day 3.

Discussions and comments on the presentation slide by slide focused on several issues as follows:

- There is a suggestion to review the proportion (trends) of patients under AL on Day 2 and Day 3 from studies carried out from 2003-2005 (when AL was first introduced) to assess trends over time in selected provinces;
- There is an observed gradual increase in Pf cases since 2005, whereas Pv is stable, similar to the number of cases in 2003. But it was easier to enrol cases in 2003 as compared to 2008. The answer was that most cases who are currently detected by mono Pf RDT reported by village health volunteers are located in very remote areas with difficult access to health care facilities. Since they use Paracheck® RDT nationwide, *P. falciparum* cases are increasingly reported. The combo Pf/Pv RDT is used only in TES sites;
- Private sector health providers also underwent training on RDT and Coartem® drug use, hence they are more accessible to patients. Training sessions targeting private sector practitioners were piloted in 6 provinces in 2007.
- Earlier studies on AL and artesunate+mefloquine (A+M) studies in 2000-2003 showed 93-100% and 100% efficacy, respectively, but AL was instead chosen as 1st line drug in Lao PDR in 2003. The reason why AL was chosen versus A+M is because GMP A-M was almost impossible to be procured at that time while co-formulated AL was made available straight from WHO at a lower cost, and was a GMP certified drug as required by both WHO and the Global Fund;
- There is no solid data and no studies showing % compliance to the 3-day BID treatment with AL. There are also no pharmacokinetic/bioavailability studies comparing AL levels in patients with food intake or no food intake. The 6.7% AL failures in 2003 was attributed to low fat intake of patients from ethnic population groups that were included in that study;
- There is no efficacy study to date on the 2nd-line treatment Quinine+Doxycycline.
- There is no result yet on chloroquine efficacy in *P. vivax* infections since not enough patients could be recruited;
- Primaquine is not used in Lao PDR either as single dose treatment for falciparum cases or the 14-day anti-relapse treatment for vivax cases due to the >20% prevalence of G6PD deficiency in the country, and reports of severe haemolysis in the 80s (based on old studies);
- An issue raised was the relationship between CMPE and the Wellcome Trust research group in Savanakheth province. Savanakheth province is one of the sentinel

provinces, but there are (apparently) no official reports from the group since the last published clinical trials with A+M in 2002, AL vs A+M in 2003-2004 and DHA-PIP in 2004. The CMPE collaborator working with them mentioned that the AL vs A+M study was extended for 2 years from 2005 to 2007 to achieve the required sample size, but no report is yet available. A study with AL+vitamin B1 has started in 2009. There are questions raised whether Wellcome Trust supported *in vivo* studies are using the 28/42-day WHO *in vivo* protocol, and whether the national ethics committee gets an update from the research group;

- A question/suggestion was raised for a senior staff from the national malaria control program to be a member of the national ethics committee to review malaria research protocols as necessary (not only in Lao PDR but also the other countries);
- A suggestion was also made to request for preliminary results from the TES studies in Savanakheth province even if it did not achieve adequate sample size, as any report of > 10% failures could flag early enough problem areas in the country;
- How are the village surveys done? ACD? Frequency? Cost? Screening criteria for village and for patients? And what is done after the survey, how is the data analysed? A suggestion was made to write the SOPs of the village surveys and costs incurred depending on duration and population size;
 - o PI from Cambodia cited his experience that cases detected by village health volunteers (VHV) are twice more than those at health centers. This then allows the program to identify high prevalence villages and they proceed to follow-up cases in these villages.
 - o PI from Myanmar recruits cases by village to village screening, choosing the high prevalence villages, and then patients are sent to the district hospital for TES enrolment.

(2) Operational Challenges to perform *in vivo* TES in the GMS (Dr Dorina Bustos)

The presentation focused on the commonly encountered problems in selected sections of the protocol, and operational challenges in the implementation of the TES by the different countries.

2.1 On issues pertaining to the protocol and requirements by the WHO Ethics Review Committee (ERC):

- The full protocol (using updated WHO template) must be signed by Principal investigator and endorsed by the Director of the Institute (WPRO requirement) separately, and include
 - o approved budget (by WHO) and other funding sources if any
 - o treatment drugs: correct dosages, drug QA, cite manufacturer, lot no., date of manufacture, expiration date
 - o all Annexes: drug dosage, AE form, CRF, etc
 - o Case report forms (CRF); *translated to local language if required by country*
- Informed Consent (ICF) in English and local language
 - o Need for child assent and pregnancy test assent forms

- Full ICF with local translation (some countries abbreviate the local translation)
- Clearance from the national or institutional ethics committee to be submitted to WHO ERC
 - Local translation of the full protocol required by some ECs

Instead of presenting a checklist, the template of the protocol was presented highlighting the sections which are very often missed or filled up incompletely by the country PIs. All these were again checked on Day 3 during the country presentations of their respective protocols.

2.2. On issues pertaining to administrative and technical constraints in the implementation of the TES, the following were discussed:

- Timing of study affected by delays in ERC approval and budget release,
- Sample size cannot be achieved within the specified study duration,
- Limiting factors: age limit set by ERCs,
- PIs to give quality time in TES field supervision and monitoring,
- TES staff re-training and microscopy refresher courses needed specially in sentinel sites with new staff,
- To ensure DOT specially for AS 7-day treatment, affix signature of staff administering the drugs on the CRF from day 0 to day 6,
- Laboratory
 - “WHO accredited microscopists” level 2 or above to do slide validation and parasite counting on site and level 1 to internally cross check TES results. Review the country list and assign them to the TES sites.
 - Have a separate logbook on slide validation
 - Develop microscopy SOPs.
 - Correct PCR and PK sample collection and storage.
 - In vitro procedures: cite drugs to be tested and which samples.
- Improvements to be made in data management/entry:
 - include all patients that have been enrolled in the Excel sheet, even those lost to follow-up or vivax infection.
 - Enter data in chronological order as they were enrolled.
 - Ensure accuracy of data entered as reported/written on the CRF.
 - Timely data entry and data validation.
- Clinical trial registration is mandatory through free websites either www.anzctr.org.au or www.clinicaltrials.gov.
- National program TES staff to be trained on Quality Control procedures in general:
 - Conduct training on **Good Clinical Practice (GCP)** and **Good Laboratory Practice (GLP)** for TES investigators and staff.
 - The “non-expert” microscopists and other provincial microscopists assigned to the sentinel sites must undergo re-training and if possible, the **External Proficiency Assessment (ECA)** to ensure QA in malaria diagnosis and counting.

(3) Collaboration with donors, Institutions and partners (*Dr Charles Delacollette*)

- Dr C Delacollette updated PIs on potential technical areas of collaboration with partners and Research Institutions in light of new global partnership network on drug resistance like WWARN or regional Molecular Markers network coordinated by the University of Maryland (C. Plowe) or to support pharmacokinetic studies with MORU (MORU, Bangkok). There is a Memorandum of Understanding between Oxford (where the secretariat of WWARN is established) and WHO Geneva to contribute to the following activities of WWARN: a) Participation of WWARN members in workshops / meetings organized by WHO to promote WWARN activities, b) For WHO to promote country data sharing with the global database maintained by WWARN, c) Disseminate agreed upon samples (for in vitro TES, exploration of Molecular Markers and pharmacokinetic studies) from TES to WWARN reference labs, d) Organization of technical meetings on an ad-hoc basis with technical support of WWARN,. Pertaining to data sharing with WWARN, it has been suggested that WHO validates the data before global sharing or publication except if national programmes think otherwise. The general concept of WWARN is to create a global network of scientists using similar protocol with data quickly posted on the WWARN website in such a way that information is available quickly and processed in a standardized fashion. The University of Maryland represented by C. Plowe is part of WWARN and has been selected by USAID RDM-A as one of the core MMP partners to explore potential markers of artemisinin resistance in the GMS e.g. as part of in vivo TES supported by WHO [but not only]. The main TORs of the University of Maryland is to provide technical support to malaria programmes to perform PCR / genotyping analysis up to international standards which includes capacity building of PIs / national staff, improvement of laboratory procedures and development of SOPs. It has been reiterated that PCR has to be used first to differentiate recrudescence from re-infection when LTF are noticed during in vivo TES. In addition, and in close collaboration with programmes, additional filter papers or venous blood sample can be processed preferably at country level or in reference labs to look at molecular markers / genes flow or assess concentration of anti-malarial drugs like artesunate in blood at regular interval (pharmacokinetic studies). It has been reiterated that countries and programmes remain the primary owner of data and results with WHO collaborating with them to generate quality data and results to carefully inform policy decision in a timely basis. It has been reminded as well that ethical clearance is needed for any deviation from the routine protocol when additional blood samples are requested.

Day 2 - March 24

(4) Experience in Thailand pertaining to follow-up of all positive cases in provinces bordering Cambodia *(Dr Kanungnit)*

Thailand has been using Atovaquone-proguanil (Malarone™) as 1st line drug in 2 districts of the containment zone 1 bordering with Cambodia (provinces of Chanthaburi and Trat), mainly to slow down the “pressure” of artemisinins derivatives on local parasites. There is a full budget provided for the field staff to allow them to follow-up cases individually on schedule during the follow-up period, up to Day 42 for falciparum cases and Day 90 in vivax cases. The recruitment centers include the malaria clinics manned by NMCP staff, the malaria posts manned by Global Fund- and Bill and Melinda Gates Foundation (BMGF)-supported staff, and the government provincial or district hospitals. Every positive case is investigated and enrolled. But if the patient refuse the follow-up or can't return to the clinics (mobile population), such patients are not enrolled and receive instead A+M for treatment.

In Zone 1, an on-line real-time malaria reporting system (funded by BMGF) using web-based technology, smart phones, GPRS network and Google Earth program has been established by the Mahidol University Faculty of Tropical Medicine under the supervision of Prof Pratap Singhasivanon and staff from BIOPHICS, as part of the containment effort. It records all data on the patient and his/her follow-ups, residence, drug compliance and treatment failure, and allows the geographical mapping of the disease in terms of time, parasite specie, infected population and the geography of disease occurrence.

It is the first time that Malarone™ is distributed under strict supervision at peripheral level, hence it was used only in Thailand where the existing performing health infrastructure and vertical programme can ensure the highest level of DOT and follow-up of patients until the end, which, however, could not be ensured on the Cambodian side. Malarone™ is not a registered drug in Cambodia, hence they used DHA-PIP. The screening system being used in Cambodia encountered many challenges: there were many asymptomatic cases that were missed, RDT and PCR were not working properly as desired, and there was too much mobility of the people that they could not be followed up as scheduled or were subsequently lost to follow-up.

The VBDC of Thailand has a computerized health reporting system wherein the information technology was further enhanced for this containment project. However, it remains to be seen how soon the IT can be institutionalized into VBDC from the Mahidol Trop Med set-up at the end of the project (Oct 2011).

(5) Country presentations on improving internal and external microscopy as part of the TES in the GMS: the way forward

Cambodia – Dr Leang Rithea

The human resources in slide quality control include:

- Two qualified microscopists per field site
- Three qualified microscopists (WHO accredited experts) in the project

All blood slides are read independently by two qualified microscopists and the second reading will be done when the discrepancy level of parasites counts exceed 50%. The third qualified microscopist reads when there is still a substantial discrepancy among the two raters. In this case the parasite count is the average of two most comparable counts among the three raters. In exceptional case, the fourth rater will be considered when the disagreements among the three raters are greater than 50%.

One expert is recruited for the whole study period for the refresher courses, monitoring the laboratory work on site and works as slide validator. Three experts in the project validate all blood slides from D0, D1, D2, D3, D4 and Df (Day of failure) and cross check 10% of blood slides from in between (D4 & Df).

Lao PDR – Dr Viengxay Vanisaveth

In 2009, Laos has six “expert” Level 1 microscopists, two Level 2 and three Level 3 microscopists. All malaria slides from the provincial level (provincial Hospital, district hospital and army hospital) are sent to province malaria station for cross checking every month, and the province sends false pos. and neg. to regional for checking every quarter, then evaluation and feedback is done. The regional level expert microscopist cross-checks the slides from the provinces and if the result is different from the province, that slide is sent to CMPE to be checked and a feedback is made.

The PI did not present quality control of TES slides and whom among the “expert” microscopists, if any, are assigned in the sentinel provinces.

Myanmar – Dr Myat Phone Kyaw

In Myanmar, a one-week refresher microscopy is done prior to the start of the TES. Per TES team in the sentinel site, there is a Medical Officer, a field microscopist, a validator microscopist, and an umpire (third independent microscopist). Two qualified microscopists need to read all of the slides independently and parasite densities should be calculated by averaging the two counts in the field. Blood smears with discordant results (differences between the two microscopists in species diagnosis, or differences in parasite density of >50% or difference in the presence of parasites) need to be re-examined by the umpire, and parasite density will be calculated by averaging the two most concordant counts. Two qualified microscopists have been required to check all slides in the field as most of the study sites have transportation difficulties during the raining season that slides cannot send back to DMR or VBDC on time.

Following the TES results from Kawthaung TES sentinel site, an external slide validation was done on 13-20 December 2009 where an expert microscopist from the Philippines cross-checked the Day 3 and Day 28 slides from this site. The internal and external slide validation results for species diagnosis and differences in parasite density was <10%.

Thailand – Dr Kanungnit

In Thailand, before the start of TES, a refresher microscopy training each year is done, and the training must include blood collection, film preparation, staining, examining and reporting. Microscopy SOPs on the slide collection and staining procedure with Giemsa stain is available in the laboratory. The 1st microscopist at malaria clinic examines the presence or absence of parasite and differentiation of parasite species. The 2nd microscopist at the regional office (Office of Disease Prevention and Control, ODP), checks the presence of parasite, differentiation of parasite and counting. And a 3rd microscopist at the Bureau of Vector Borne Disease (BVBD) checks again the presence of parasite, differentiation of parasite species and counting. If there is discordance on the presence of parasite or parasite species, the expert microscopist level 1 at the BVBD will check again and conclude the results. The counting of the 2nd and 3rd microscopist should not be different by more than 25%. If the counting is different by more than 25%, it will be counted by the expert microscopist level 1 at the BVBD. The counting is the average of the pair that the difference is not more than 25%.

Supervisory visits are done initially before the study and at least 2 times for each sentinel sites during the study, with random checking of the slides. As part of the External QA program, there is a plan to have the expert microscopist level 1 from the Faculty of Tropical Medicine or AFRIMS or other country to check the TES slides.

In the methods for counting:

- 100 HPF examined before declaring NPS
- Count to ~ 200 WBC, if 100 or more MP counted then perform the calculation
- If at ~ 200 WBC less than 10 MP counted, continue counting to ~ 500 WBC, then perform calculation.
- All WBC and MP counted in the final field.
- In traversing the thick film, start the count in the top left hand section of the film, and move in a cross-sectional manner.
- Continue counting in fields, approximately 5 fields apart, with or without WBC and/or malaria parasite.

Viet Nam – Dr Ta Thi Tinh

As part of the regulations of the NMCP for slide Quality control, all positive slides have to be sent to higher level for QC; 10% of negative slide are requested to be sent to higher level for QC; and the result of QC will be officially sent to sender within one month after receiving slide.

For the internal QC of TES slides, all TES microscopists have to be retrained on parasite counting. Two microscopists count parasites independently and the expert microscopists will read if there is > 50% difference between the counts of the two microscopists. In the external slide validation of TES slides from Binh Phuoc in 2009, an expert microscopist from Cambodia came. There was almost 100% agreement in the readings of the expert and the Vietnamese microscopists for the Day 3 and Day 28 positive and negative slides, except for one Day 3 slide with a very low parasite count.

In the 2009 External competency assessment (ECA) done by ACTMalaria and WHO, Viet Nam now has six level 1 microscopists, four level 2, and two level 3 microscopists. To further improve QA of TES slides, the plan is to have microscopists level 1 in the field, and microscopists level 2 must have passed the ECA course by ACT-WHO. For Day3 and Day of failure slides: 100% slides will be cross-checked by 3 institutes, and 10% slides of Day 28 slides will be cross-checked.

In the ensuing discussions, it was explained that the External Competency Assessment (ECA) conducted per country on a regular basis by Maj. Ken Lilley from the Australian Army Malaria Institute with the support and coordination of ACTMalaria and WHO, ensures a high level standard of competency among malaria microscopists in the region. Level 1 experts must have >90% accuracy in specie identification and >50% correct parasite counts within 25% of the true count. It has the following grading scheme:

Table 1: External Competency Assessment (ECA)

Final Assessment Grades for Expert Accreditation		
Grading Group	Species Identification (Accuracy)	Parasite Counting (within 25% of the True Count)
Level 1 – Expert	90%	50%
Level 2 – Reference	80%	45%
Level 3 – Advanced	70%	30%
Level 4 – Training	<70%	<30%

NMCP microscopists must undergo said ECA every 3 years, as this accreditation is valid for 3 years only. All the GMS countries are provided their list of Level 1-4 microscopists since 2005. In the past 2 years, as observed by this author during the 2008-2009 monitoring of the TES sites, none or very few of these experts are involved in the TES per country. They are assigned in some other provinces, or at the central level, or some other projects and research institutions.

Since this is an established standard of highly competent microscopists and there are already several experts per country, it is proposed that countries involve said “*WHO accredited microscopists*” in the TES sites as the slide validators.

(6) Pragmatic Data Quality Management for Malaria Surveillance Studies *(Trudie Lang)*

The concept of total quality management (TQM) was introduced, highlighting the importance of GCP in clinical trials. Developing a Quality Management plan is a straight forward operational plan to confirm data reliability and high ethical practice for any type of clinical research. It can be written for single or multi-centre studies. It is important that is designed specifically for each study to ensure it is appropriate as agreed upon and achievable, and written by those running the study to reflect true situation and capacities. The East African network with over 20 studies was cited as an example, where all participating research groups and over a hundred staff benefited after a training in quality management. All studies now have QM SOP and all have this reviewed and checked, with wide reaching benefits from sharing best practices and learning from each other. It is straight-forward, in-expensive and highly regarded.

The potential benefits of a reciprocal quality management were further explained. It offers a simple mechanism for putting a QM system in place. It allows sharing of best practices and standardisation between sites in a region, country or network. It gives those trained a new dimension to their roles and provides new skills and training. Sites get their studies quality assured and there are experience benefits of staff being exposed to training and other research sites.

In summary, quality management is important for any type of research to ensure good data and high ethical standards. It is important in the GMS region as such a key question is being asked of drug efficacy in this region. A good starting point is writing a quality management plan for the studies (guidance and template provided). A potential mechanism could be for sites to agree to perform quality management visits for each other – reciprocal quality management. This would bring credible QM alongside wider benefits of improving networking and sharing skills and standards. WWARN will be happy to provide ongoing support, guidance and tools and can also provide training through their wider network.

(7) Field visit

The afternoon of Day 2 was spent on a field visit to Nane District Hospital (a malaria surveillance site) and the Nane Health Center along the way.

Observations/discussion:

- there have been no malaria cases in the Nane District hospital since 2008
- the laboratory uses both RDT and microscopy
- there are 6 health centers in this district and only 1 has a microscope
- since 2000, the hundred of hectares of forests have been burned and converted to rubber plantations by Chinese companies; its impact on malaria transmission and vector bionomics is not known.
- Local health workers are reporting that Chinese workers brought in artesunate monotherapy drugs (from China) and made monotherapies available also to their Lao migrant workers in the farms. Those monotherapies can be bought from the private

local stores (we requested to see some samples but there were none available in the hospital)

- according to the district hospital head, the Lao health workers have trained clinic staff in one rubber plantation farm to do RDT and they also provided Coartem® for treatment.

Nane Health Center:

- this is a newly opened health centre, which has a mirror microscope, but is not being used for malaria microscopy
- there is stock-out of RDT since January 2010: had to discard expired RDT

Day 3 - 25 March

The Principal Investigators of Thailand, Viet Nam, Cambodia, Myanmar and Lao PDR presented their country proposals, and were commented upon by other PIs and facilitators (Charles Delacollette, Lasse Vestergaard, Dorina Bustos, Abdur Rashid and Tran Cong Dai). Sections and paragraphs where attention is needed were purposely highlighted in such a way that PIs will come up with a quasi perfect protocol with all needed annexes in the coming weeks.

Below is a tabulated summary of the drugs to be tested and sites in 2010, and other country specifics.

Table 2. Summary of current status of proposals of the 6 GMS countries (5April 2010)

2010	Thailand	Myanmar	Cambodia	Viet Nam	Lao PDR	China
Pf sites and drugs	A+M Tak, Yala, Ratchaburi, Ranong	DHA-PIP, AL Yakhine, Kayin, Mon, Kalay Eastern Shan AS7 Kawthaung	DHA-PIP, A+M, AP, ASMQ Pailin, Rattanakiri, Snoul- Kratie	AS7 - Dak Nhau, Bin Phuoc - Dak Nong DHA-PIP - Quang Tri - Gia Lai	AL Luang Prabang (Chompet or Ngoy District +2 HCs + villages) Khammoune Attapeu	AS7 Dehong DHA-PIP Menglian
Pv sites and drugs	CQ Mae H Son Kanchanaburi	CQ Yakhine Kayin and Mon State	CQ	CQ Quang Tri		CQ Jiangsu
Age	≥ 6 months	≥ 6 yrs old	2-60 yrs	2-60 yrs old		≥ 6 months
Sample size	50 patients	80 each arm	50 patients	Pf = 60 patients Pv = 42 patients		60 patients
In vitro	NA	NA	NA	Binh Phuoc	NA	Yes
Drug QA	AS, Mef, CQ procured by VBDB: AS send to WHO Collaborating	DHA-PIP and AS7 to be provided by WHO; AL from NMCP	DHA-PIP, AP, CQ, AS+M from WHO:	AS7 to be provided by WHO; Arterakin to be QA tested at	AL procured by the NMCP	DHA-PIP, AS7 and CQ to be provided by WHO

	Center, Nat'l Institute for Drug Quality Control, Hanoi, VN	procurement	ASMQ from DNDi	WHO Collab Center, Nat'l Institute for Drug Quality Control, Hanoi		
ICF translation	Yes	Yes	Yes	Yes		
Ethics clearance	Pending	Pending for AS7	Pending	Pending		
PR review proposal	Yes	Yes		Yes		
Covering memo	Pending	Pending	-	-	-	-
Country-specific issues		3 separate protocols: 3 sites in upper Myanmar; 2 sites Lower M; and AS7 in Kawthaung	Sites and drug to be decided on April 2010 drug policy meeting		Protocol and ICF to be written	Protocol not presented (emailed recently)
Duration	April-Dec 2010	May-Oct 2010	June-Dec 2010	Aug-Dec 2010	Start Q4 2010	June-Dec 2010
Total Budget	US\$78,438	- 3 sites LM: US\$68,330 - 2 sites UM: US\$61,430 - Kawthaung: US\$20,850	Pending	US\$60,000	Pending	US\$103,000

Other issues discussed and settled:

1. unmarried pregnant women 12-18 years old are excluded
2. It was suggested to do the 42-day follow-up in all countries assessing DHA-PIP and A+M (this will include VNM, CAM, CHN, MMR and THAI)
3. For parasite counts, the country will decide whether to use the white blood cell density of 6000 or 8000 according to microscopists' training
4. All countries must register their clinical trials
5. The Ministry of Health is the sponsor (not WHO).
6. Thailand and Myanmar will send their complete proposals to ERC HQ with cover memo letter, and all the others will send to WPRO with the 2-page cover sheet specific for WPRO.
7. Cambodia will decide what drugs to test in which sites after the drug policy workshop in April 2010.
8. Country budgets will be discussed further with Dr Charles Delacollette, Dr Eva Christophel and Pascal Ringwald.
9. Country PIs were advised to include in the budget section other non-WHO funds intended for TES, with a brief description which drugs and in which sites these

- will be done. This is to allow WHO to understand where other therapeutic efficacy studies are carried out and by whom in the GMS.
10. It was re-emphasized that the complete protocol and informed consent forms must be submitted to WHO together with national or institutional ethical clearance.

Presentation by Lao PDR

With the inability to recruit adequate number of patients in the 3 sentinel sites in Laos in 2009, the Lao TES team came up with the following decision points:

- Move sentinel sites to other provinces with higher disease burden, based on available case reports
- In these new provinces, identify 1 District Hospital and 2-3 nearby Health Centers covering strata-3 villages
- Ensure expert microscopist to be based on a daily basis in District Hospital + Health Centers
- Expand patient recruitment criteria (lower parasite density) + extend study period
- Ensure very effective patient follow-up!

The existing template will be used, but will maximize the limits and resources and increase budget to enroll patients:

- All patients > 6 months eligible, pregnant women excluded
- ALL microscopy-positive cases to be enrolled - irrespective of parasite density (if follow-up considered feasible)
- Patients to be enrolled from as many health centers in the district as possible, considering feasibility and costs
- ALL slides from Health Centers to be checked by Level 1 Microscopists at District Hospital for parasite density – patients to be excluded retrospectively if parasites < 250 per microlitre
- Strong emphasis on high-quality microscopy + external validation!
- Study period extended to 12 months (to cover two peak seasons)
- Field staff needs to be very active in case follow-up, equipped with motorbikes
- Health Centre Microscopists to cover neighboring Health Centers if feasible, equipped with motorbikes
- Very close communication between District Hospital and Health Centre teams, monitored and supervised by Provincial Malaria Team

There will be tentatively 3 sites:

(1) the northern Lao PDR sentinel site, will have several catchment centers:

In Chompet District, there was malaria epidemic in 2009: 210 cases in Oct-Dec 2009, Jan-March 2010 22 cases, severe cases including one death reported. This is very close to Luang Prabang town center. An alternative is Ngoy district, but farther from the center.

- Total population of 1,315 living in 4 strata-2 villages (2008) in Chompet
- Total population of 1,438 living in 3 strata-3 villages (2008)

Two Health centers identified are possible catchment centers:

- Nong Pout

- Nagew

Microscopy expertise:

- Level 1 Microscopist already available in Province, can easily work at Chompet District Hospital on a daily basis
- Two additional Level 2 Microscopist needed to be based 12 months at involved Health Centers + cover neighboring Health Centers if feasible

(2) Khammoune province in central Laos

Xaibouatong District Hospital

- Covers a total population of 1,983 living in 9 Strata-3 villages (2008)

Health Centres selected:

- Na-Noi
- Khangchoin

Microscopy expertise:

- Level 1 microscopist already available in Kham Mouane Province, who can possibly be stationed at Xaiboutang District Hospital for a 12 months period
- Two additional Level 2 Microscopist needed to be based 12 months at involved health centers + cover neighboring Health Centers if feasible

(3) Attapeu province in southern Laos

Samakkixay District Hospital

- Total population of 11,875 distributed in 16 Strata 3 villages (2008)

Health Centres selected:

- Khoomkham
- Bengphoukham

Microscopy expertise:

- Level 1 microscopist already available in Attapeu Province, can likely be stationed at Samakkixay District Hospital for a 12 months period
- Two additional Level 2 microscopist needed to be based 12 months at two health centers + cover neighboring health centers if feasible

Proposed timelines for revised TES in Lao PDR, 2010:

1. Revised TES protocol and budget to be finalized and submitted for ethics approval during April-May 2010
2. Training of Provincial Malaria Team + Clinicians + Nurses in revised TES methodology, June-July 2010
3. Training of microscopist, July-August 2010
4. Practical and logistical arrangements to be sorted out, July-September 2010
5. Studies to start 1st October 2010 in all three provinces

Conclusions

- All 5 countries presented their country proposals for 2010 using the WHO template, including Lao PDR, who proposed to start recruitment by November 2010. Comments, edits, recommendations were made for each country proposal to conform to WHO ERC requirements. Table 2 above gives a status summary per country. The Thailand proposal is ready to be sent to HQ pending local ethics committee clearance. All other proposals need more work and refinement and local EC clearance.
- The proposal from China was sent by email and needs to be edited (done and sent back to China as of this writing).
- It was agreed upon with the PIs that the microscopists who have undergone the ECA from 2007 to the present, and are the *“WHO accredited microscopists”* will be assigned in the TES sites as the slide validators.
- Lao PDR presented an alternative option to the classic sentinel site approach. There will be 3 sentinel sites :
 - a regional site in the north, encompassing 1 province (Luang Prabang) with the involvement of provincial and district hospitals (Chompet and Ngoy District Hospital, health centers and village volunteers in patient recruitment).
 - one province each in central Laos (Khammoune)
 - and southern Laos (Attapeu) + a district hospital and HCs at the village level
- The regional site will Study duration was extended to 8 months in order to capture 2 peak transmission periods (to be carried out every 2 years).
- It was planned to maximize the use of the protocol accordingly (i.e. lower parasitemia in all patients), use the “WHO accredited” microscopists in the district hospital sites to ensure the parasitemia
- Provide an adjusted budget estimate (still to be prepared) to be submitted to WHO to be able to start by November for the 2010 TES country plan.

Recommendations

- National program TES staff to be trained on Quality Control procedures in general:
 - Conduct training on **Good Clinical Practice** (GCP) and **Good Laboratory Practice** (GLP) for TES investigators and staff
 - Budget to be identified

- The “non-expert” microscopists and other provincial microscopists assigned to the sentinel sites must undergo re-training and if possible, the **External Proficiency Assessment** (ECA) to ensure QA in malaria diagnosis and counting
- It was suggested by one of the external validators to Myanmar (Mr Sherwin Galit), that TES microscopists develop the laboratory SOPs and follow a standard for parasite counting. This can be done with the lead participation of the PI from Thailand, Ms Kanungnit, as she recently passed the ECA this January 2010, and is familiar with TES requirements. This is also to help resolve the very low parasitemia discordance between readers.
- It is still necessary to give technical assistance/mentoring to some countries in writing up the protocol and always check the informed consent forms and the local language translation.
- The country PIs can do cross country monitoring visits to observe project implementation and best practices.

ANNEX 1. Agenda

Workshop for the “Development of a District Based Treatment Efficacy Study (TES) Protocol for Antimalarials”

23 – 25 March 2010

Vang Thong Hotel
Luang Prabang, Lao PDR

FINAL AGENDA

March 23rd (DAY 1)

8:30	Registration of participants	
9:00	Welcome remarks	<i>WR Lao PDR</i>
9:05	Introduction of participants	
9:10	Nomination of chairperson and rapporteurs Review of the draft Agenda and expected outcomes ³	<i>C. Delacollette</i>
9:20	Technical challenges and options to perform <i>in vivo</i> TES in Lao PDR	<i>V.Viengxay</i>
10:00	Coffee break and group photo	
10:30	Questions, Clarifications and discussion	
11:00	Updates of main challenges to perform <i>in vivo</i> TES in the GMS	<i>D. Bustos</i>
11:50	Collaboration with donors, institutions and partners on Molecular markers in vitro studies, and pharmacokinetics:	<i>C. Delacollette</i>
12:30	lunch	
14:00	Experience in Thailand pertaining to the following-up (28-day) of all positive cases in provinces bordering Cambodia	<i>Kanungnit</i>
14:30	Plenary discussion on options / protocols to perform <i>in vivo</i> TES in low transmission settings	<i>Plenary</i>
16:00	Coffee break	
16:30	Preliminary conclusions	
17:00	Closure of DAY1	

³ *Extra technical sessions were organized with Lao team to draft the revised district-based TES protocol*

March 24th (DAY2)

- 08:30 Improving internal and external QC microscopy as part of TES in the GMS:
the way forward (15 min+ 5 min clarification per country)
- Cambodia
Lao PDR
Myanmar
Thailand
Vietnam
- 10:00 Coffee break
- 10:30 Suggestions to improve quality microscopy as part of TES *Plenary*
- 11:00 Reciprocal Quality assurance tool as a mean to improve quality data
generated by TES *Trudie Lang*
- 11:30 Clarifications and discussion *Plenary*
- 12:00 Lunch
- 13:00 Field visit to Nan district (malaria sentinel surveillance site)
- 18:00 Closure of day2

March 25th (DAY3)

- 8:30 Country proposal presentation by each PI (30 minutes each) *Cambodia, Myanmar
Viet Nam*
- 10:30 Coffee / tea break
- 11:00 Country proposal presentation *Thailand*
- 11:30 Plenary discussion
- 12:00 Next steps *C. Delacollette*
- 12.30 Lunch
- 14:00 Closing remark and closure of the meeting *Chairperson*
-

Workshop for the Development of a District-Based (TES) Protocol to Monitor Therapeutic Efficacy of Antimalarials in Lao PDR

**23 – 25 March 2010
VangThong Hotel
Luang Prabang, Lao PDR**

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