METHODS AND TECHNIQUES FOR CLINICAL TRIALS ON ANTIMALARIAL DRUG EFFICACY:

genotyping to identify parasite populations

Informal consultation organized by the Medicines for Malaria Venture and cosponsored by the World Health Organization

29–31 May 2007, Amsterdam, The Netherlands

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ABBREVIATIONS USED

bp	base pairs
csp	gene of the circumsporozoite protein
EDTA	ethylene diamine tetraacetic acid
DNA	deoxyribonucleic acid
glurp	gene of the glutamate rich protein
MR4	Malaria Research and Reference Reagent Resource Center
msp1 & *2*	gene of merozoite surface protein 1 & 2
nPCR	nested polymerase chain reaction
PCR	polymerase chain reaction
pPCR	primary polymerase chain reaction
resa	gene of the ring-infected erythrocyte surface antigen
RFLP	restriction fragment length polymorphism
RNA	ribonucleic acid
RT-PCR	reverse transcription-polymerase chain reaction
SSCP	single-strand conformation polymorphism
trap	gene of the thrombospondin-related adhesive protein
WHO	World Health Organization

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EXECUTIVE SUMMARY

The treatment outcomes in trials of antimalarial drug efficacy are classified on the basis of an assessment of parasitological and clinical effects. Estimates of success are calculated as the percentage of patients who show an adequate clinical and parasitological response before and after adjustment by polymerase chain reaction (PCR) for likely reinfection.

PCR adjustment of cure rates initially based on blood-slide microscopy and clinical assessment, is necessary because, particularly in areas of high malaria transmission, super-infection with additional parasites occurs frequently during the follow-up period of trials, owing to their long duration. Towards the end of the treatment period, antimalarial drug levels can fall below curative levels, allowing new infections emerging from the liver to establish themselves.

Thus, PCR-corrected cure rates have become accepted as the end-points in regulatory clinical trials and for monitoring antimalarial drugs. In the past, there was considerable variation in sampling procedures, genotyping techniques and interpretation of data. To achieve harmonization, the Medicines for Malaria Venture convened a meeting, cosponsored by the World Health Organization (WHO), of experts in the field of *Plasmodium* genotyping. The aim of the meeting (held in Amsterdam on 29–31 May 2007) was to achieve consensus on standard operating procedures that would be applied in all specialist malaria genotyping laboratories. The procedures were designed to be used in national malaria control programmes for routine monitoring of the efficacy of antimalarial drugs, by teams researching and developing antimalarial drugs in clinical trials conducted for regulatory purposes, and more generally for clinical research. The meeting agreed to the following definitions:

- A 'new infection' is a subsequent occurring parasitaemia in which all the alleles in parasites from the post-treatment sample are different from those in the admission sample, for one or more loci tested