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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WHO Library Cataloguing-in-Publication Data

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.

1.Antimalarials - therapeutic use. 2.Antimalarials - administration and dosage. 3.Antimalarials - standards. 4.Clinical trials. I.Medicines for Malaria Venture. II.World Health Organization.

ISBN 978 92 4 159630 5

(NLM classification: WC 770)

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Design & Layout by WHO Graphics Printed in France

ABBREVIATIONS USED

base pairs
gene of the circumsporozoite protein
ethylene diamine tetraacetic acid
deoxyribonucleic acid
gene of the glutamate rich protein
Malaria Research and Reference Reagent Resource Center
gene of merozoite surface protein 1 & 2
nested polymerase chain reaction
polymerase chain reaction
primary polymerase chain reaction
gene of the ring-infected erythrocyte surface antigen
restriction fragment length polymorphism
ribonucleic acid
reverse transcription-polymerase chain reaction
single-strand conformation polymorphism
gene of the thrombospondin-related adhesive protein
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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

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