1. This was a placebo-controlled study in patients with acute, sometimes severe malaria. How were the ethical concerns assessed and resolved in this trial?

The intervention was trying to improve early care for patients who live in remote areas and have no clinic or hospital nearby. These patients often die because treatment is too late. In the remote areas of the trial conducted in 291 communities in Bangladesh, Ghana and the United Republic of Tanzania, all patients were randomly treated in their village with either an artesunate or placebo suppository and then immediately referred to a hospital or clinic for follow-up. To facilitate compliance with referral advice, transport to a referral hospital or clinic was offered to trial participants in Ghana study sites. In the United Republic of Tanzania, district hospital and health centres in the study communities were strengthened in terms of personnel and commodities; and, as per Government policy, children under the age of 5 years were exempted from any hospital or clinic costs. In Bangladesh, special arrangements were made with referral hospitals to assure that trial participants would have immediate free hospitalization and any required medications available. Compliance with referral advice was high: exceeding 87% in Africa and 98% in Asia. Median time to arrival at hospital was 2 hours in Bangladesh and 3–4 hours in African sites. As a consequence of study participation, each patient had a better chance of care and survival – regardless of whether they were administered rectal artesunate or placebo.

Permission to conduct the studies was sought and obtained from: 1) the ethics and research committees of the World Health Organization (WHO); 2) the Ministry of Health in each partner country and national ethics review boards; 3) the study communities via informed consent processes in local languages prior to the initiation of the study; and 4) from patients and their guardians prior to treatment. The process of informed consent was scrupulously monitored by the investigators and by clinical monitors. A data and safety monitoring board regularly considered the conduct of, and data from, the study and all serious adverse events.

2. How feasible is provision of medication at the community level?

In the study, treatment was administered by 417 resident village recruiters who had little or no previous medical knowledge, and underwent one to three weeks of training. The recruiters assessed patients with suspected severe malaria, administered trial treatment, referred patients to a hospital or clinic, and followed up each patient at home. These village health workers performed a function similar to that of community health-care providers in many malaria-endemic countries. However, the training, supervision and monitoring of the resident village recruiters for the purposes of the clinical trial was more rigorous than that which would be the norm in many community settings.

3. What is the acceptability of rectal artesunate treatment?

Medicines for many common ailments are available in suppository formulations, most frequently antipyretics. Previous ethnographic research in the United Republic of Tanzania and Ghana had shown that there is local familiarity with rectal preparations,
both traditional and biomedical, and these were usually administered by mothers to their children. In the context of the trial, participants readily cooperated with this method of administration. Children were typically treated by the village recruiter, but older patients were commonly treated by another family member, either a spouse or an older woman in the case of female patients, under the supervision of the recruiter.

4. Are rectal artemisinins widely available?
Rectal artemisinin formulations (primarily artesunate, artemisinin and artemether) are produced and sold in many malaria-endemic countries.

5. Have other similar studies on rectal artemisinins been conducted, and do these results apply to rectal artemisinin products or formulations other than the one tested in this trial?
Hospital-based studies have been conducted with a range of rectal artemisinins; virtually all of those studies have demonstrated superior efficacy of the rectal product to injectable quinine in patients with severe malaria who cannot take oral medication. However, to date, no randomized-controlled studies of other rectal artemisinins in remote, community-based studies have been conducted. No study has been carried out that provides a direct assessment of bioavailability between the different rectal artemisinin-based derivatives. Therefore, equivalence could be established from these results to other products or formulations through future clinical studies that directly compare one product with another.

6. Can rectal artesunate be recommended for older patients?
The current WHO Guidelines for the treatment of malaria recommend that patients of all ages who are unable to take oral drugs be given pre-referral treatment (either intramuscular artemether, artesunate or quinine, or, if not available, rectal formulations of artemisinin or artesunate), and referred to the nearest hospital. The new evidence on efficacy and safety provided in this study will be reviewed as part of the overall evidence to be incorporated into the next edition of the WHO malaria treatment guidelines (2009).

7. Should rectal artesunate be used with diagnosis, using rapid diagnostic tests or microscopy?
Having a confirmed diagnosis of malaria is critical to the adequate treatment of the disease. It is therefore important to support and reinforce access to optimal diagnosis of clinical symptoms. At the same time, in severe malaria, the disease progresses fast and is fatal if untreated. Therefore, even if microscopic or rapid diagnostic tests are not available, the priority is still to treat and refer the patient to the nearest health centre.

8. Why it is important to refer all patients treated with rectal artesunate to either a hospital or qualified health clinic for follow-up?
Where rectal artesunate is used at community level, it is essential that referral to a hospital or clinic still take place as quickly as possible! There are two reasons for this.
   i. The artemisinins act very fast in killing parasites. Hence even seriously ill patients may begin to recover very quickly following administration, but if they do not follow up with referral to a hospital or health clinic their condition could again deteriorate without complete curative treatment.
   ii. Accurate diagnosis is often not available at community level, and there is a risk that presenting symptoms might in fact not be due to malaria, but to another life-threatening disease.

Therefore, in any deployment of rectal artesunate at community level, advocacy and educational materials should emphasize the importance of referral and follow-up
among patients and village health providers. Ideally, artemisinin-based combination therapy should also be available before the deployment of rectal artesunate in the community and clinic settings to ensure that uncomplicated malaria is treated early, and that effective treatment is available to patients treated with a rectal artemisinin once they are able to tolerate oral medication.

9. How likely is it that clinical symptoms assumed to be malaria may be those of another infection?
There is considerable overlap in the symptoms of malaria and the symptoms of other infections. Symptoms such as a high fever; inability to eat, drink or suck; repeated vomiting; repeated convulsions; altered consciousness or coma may be associated with severe malaria or with other infections, such as pneumonia, sepsis or meningitis. In some cases, a patient may have both malaria and another infection. Thus, proper follow-up and diagnosis of a patient’s condition is necessary to avoid further deterioration and possible death. This, again, underlines the importance of referral of all patients treated with a rectal artemisinin to the nearest health facility to diagnose any other infection.

For more information, please contact:
Dr Melba Gomes
Scientist, Special Programme for Research and Training in Tropical Diseases (TDR)
gomesm@who.int

For press enquiries, please contact:
Ms Jamie Guth, Communications Manager, TDR
guthj@who.int

Ms Elaine Fletcher, Managing Editor, TDR
fletchere@who.int