WHO Informal Consultation on clinical neurological investigations required for patients treated with artemisinin compounds and derivatives

Report of an Informal Consultation convened by WHO

Geneva 20 July 1998
This document is not issued to the general public, and all rights are reserved by the World Health Organization (WHO). The document may not be reviewed, abstracted, quoted, reproduced or translated, in part or in whole, without the prior written permission of WHO. No part of this document may be stored in a retrieval system or transmitted in any form or by any means – electronic, mechanical or other – without the prior written permission of WHO.

The views expressed in documents by named authors, are solely the responsibility of those authors.
WHO Informal Consultation on clinical neurological investigations required for patients treated with artemisinin compounds and derivatives

Report of an Informal Consultation convened by WHO
Geneva 20 July 1998
# TABLE OF CONTENTS

WHO informal consultation on clinical neurological investigations required for patients treated with artemisinin compounds and derivatives .......................................................... 1

Statement of issues ........................................................................................................ 1

Clinical perspective of the role of ams derivatives and a description of cerebral malaria .......... 1

Discussion of sites where special neurological studies might be carried out ..................... 3

Discussion of appropriate methods and investigations .................................................. 3

Artesunate phase IV field trials .................................................................................. 5

Retrospective studies .................................................................................................. 6

Prospective studies ..................................................................................................... 6

Information exchange ................................................................................................. 6

LIST OF PARTICIPANTS ............................................................................................ 7

Appendix 1: DISCHARGE FORM ............................................................................. 9

REFERENCES ............................................................................................................. 9
**WHO Informal Consultation on clinical neurological investigations required for patients treated with artemisinin compounds and derivatives**


**Statement of Issues**

Several compounds of the artemisinin family are being developed for the treatment of severe malaria, including dihydroartemisinin (DQHS), artemether (AM) and artesunate (AS). So far they have proved to be effective in man and to have caused few adverse effects in clinical use.

Recent experimental studies at the Walter Reed Army Institute of Research have showed that the more lipophilic artemisinin derivatives were able to produce a unique pattern of sparse, selective neuropathy in the brainstem in animals given very high parenteral doses over a short period. The ranking of susceptibility of the species examined is dog>rat>rhesus monkey. Although the pharmacokinetics of the compounds in these animals has not been characterized completely, the doses required to produce the neuropathological changes have been several-fold higher than therapeutic doses in man.\(^1\)\(^2\)\(^3\)\[^{IRR1}\]\(^4\)\[^{IRR2}\]

There is persistent neurological deficit following cerebral malaria in 3% of adults and 10% of children. In a very large number of clinical studies, some of which have included detailed neurological examinations and long-term follow up, there has been no evidence of neurological damage in patients treated with any of the compounds, not even in cases of cerebral malaria. Children have also been shown to develop normally after treatment in studies that have included specific investigations of neurobehavioural development.\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)

Because of concern about the possible risk of neurotoxicity, a WHO Informal Consultation was arranged to review and outline appropriate future clinical studies to rule out neurotoxicity in man. The specific objective of the consultation with neurology and other experts was to plan appropriate strategies for investigations at the bedside and in more sophisticated facilities.

Professor Dayan opened the meeting by stating that neurotoxicity has been seen in a number of animal studies with high dose, parenteral administration of lipid-soluble artemisinin (AMS) derivatives, but not after oral administration. It is considered that water soluble compounds (e.g. artesunate) are generally less toxic and have not been shown to produce neurotoxicity in animal experiments. There is no single, typical neurological syndrome that characterizes the terminal stages of AMS toxicity in animal studies. Neuronal damage was characterized by chromatolysis and necrosis of a few scattered neurons in certain brainstem and cerebellar roof nuclei.

**Clinical perspective of the role of AMS derivatives and a description of cerebral malaria**

Professor White and Dr Hien provided background information from a clinical perspective. Artemisinin derivatives (based on the DHQS structure) were developed in China in the early 1980s. Therapy with artemisinin derivatives was introduced in Viet Nam in 1989, when 1 million cases and 3-4000 malaria deaths occurred each year. A double blind study conducted between 1993 and 1996 in the Centre for Tropical Diseases, Ho Chi Minh City, compared intramuscular artemether (AM) and quinine (QN) in adults with severe malaria. This study showed a decreased parasite clearance time (PCT), but prolonged fever clearance time (FCT) and coma recovery and also a slightly (but
non-significantly) lower mortality in the AM arm.\(^2\) No adverse effects were found in assessments, which included frequent, thorough neurological evaluations, electrocardiograms and audiometry. Results of blinded post-mortem examination of brainstems from this study are pending (preliminary results show no gross abnormalities). Since use of artemisinin and its derivatives as standard treatment was implemented in Viet Nam, fewer falciparum malaria cases and fewer malaria deaths (>3000 deaths in 1989 - 150 in 1997) have been recorded.

Cerebral malaria has a 15% mortality (despite adequate facilities and treatment), with approximately 10% of surviving children having a detectable neurological deficit, and occurs predominantly in areas of low to intermediate malaria transmission.

Millions have been treated with the AMS derivatives in South East Asia especially, and increasingly in South America and Africa; 10 - 20 000 of these patients have been followed and fully documented in prospective studies. A TDR/Wellcome Trust study in Viet Nam, which recorded AMS dose and conducted audiometry and measured auditory evoked potentials (analysis blinded), found no difference between controls (who had never received AMS) and cases. This study was repeated in Thailand, with 80 patients who had had 2 or more treatment courses. An additional 1100 cases in Thailand have had full neurological examinations, performed by physician assistants. No specific pattern of neurological abnormalities was seen in these patients. In the comprehensive clinical examinations, the only relevant condition that might have been missed because of training of the examiners was fine abnormalities of eye movements.

**General discussion and questions**

**Q: What is the nature of residual deficit observed in children with a history of cerebral malaria?**
Prof. White replied that these are predominantly ischaemic strokes, hemiplegia, cortical blindness or global deficits; less common are tremor, isolated cranial nerve palsy, or psychosis. Deafness has not been described. The natural history of the obvious residual neurological deficit is that 75% recover in one year. Subtle psychomotor abnormalities may persist. Cerebellar dysfunction also occurs and is thought to be malaria related.

**Q: Was the post malarial syndrome described in US veterans after service in Viet Nam (which responds to steroids and so may be immune related) seen in the Viet Nam RCT?**
Dr Hien replied that children who have received up to 14-15 AM doses were assessed, including Auditory Evoked Potentials (AEP), and no abnormality was found. Dr Ribeiro and Professor White added that adverse event data on 11 400 cases (1400 of whom had serial detailed neurological examinations, 600 of which were published), had been collected and no significant neurological damage had been identified.

**Q: The Vardi study showed abnormality of higher cortical function - is this part of malaria?**
In Kilifi, a 5-year follow-up included psychometric and higher function tests - unpublished results suggest borderline possibility of abnormalities.

**Q: What about quinine neurotoxicity (QN)?**
Prof. White replied that QN is cochlear poison. Dose-related reversible hearing impairment occurs in high doses. Permanent blindness (now believed to be a direct toxic effect on the retina) is well described with standard doses. It was once attributed to the retinal artery spasm. It also occurs in overdose. QN also causes hypoglycaemia by inducing hyperinsulinaemia and may thus cause neuronal damage indirectly.
Discussion of sites where special neurological studies might be carried out

Ghana site (Dr Binka):
Dr Binka described an area in Navrongo with hyperendemic malaria (mean EIR 300/year, seasonal), with 140,000 people in dispersed settlement over 1600 km², underutilized health facilities and the district hospital (2 physicians) seeing more cases than health centres, and where only gross neurological signs are noted, diagnosis is clinical, and health services are basic. Nine hundred severe malaria cases are admitted/year. The bulk of cerebral malaria patients go to traditional healers.

CDC / KEMRI, Kisumu, Kenya (Dr ter Kuile):
Dr ter Kuile described an area with intense perennial transmission and high-grade chloroquine (CQ) resistance. This centre is currently involved with:

- Hospital based studies (on the overlap of malaria and HIV in pregnancy);
- Laboratory based studies;
- Large community based studies on the effect of insecticide impregnated bednets on under-5 mortality, which is being conducted over 200 km² in a population of 120,000 (in 200 clusters).

The strength of the community-based studies is in numbers, but no system is in place to conduct a detailed neurological examination. Severe malaria presents predominantly as severe anaemia - cerebral malaria is not common.

Wellcome Trust Centre, Viet Nam (Dr Hien):
Dr Hien described an isolated area with 2-4000 inhabitants, which is poor, and with limited access to drugs. A community health station is established and a team could be sent to regularly assess patients.

Wellcome Trust Centre, Malawi (Prof. Molyneux):
Blantyre is in an area of lower transmission (with more cerebral malaria) and this centre is based in an academic hospital. Several hundred cerebral malaria cases are seen each year, and a plan to introduce magnetic resonance imaging (MRI) and computed tomography (CT) facilities in the private sector shortly has been proposed.

Discussion of appropriate methods and investigations

Two questions were addressed in this discussion, namely:

- A study to be designed specifically to exclude / define neurotoxicity in humans
- Defining what neurological assessment should be conducted in Phase 4 studies to be carried out by WHO and other pharmaceutical companies taking any one of these derivatives to registration.

The clinical investigations would be directed at the functions controlled by the specific areas in the brainstem known to be affected in animal experiments.

Professor Thomas recommended that hearing, vestibular function, RAS (alertness), and cerebellar function (control of voluntary movement) should be assessed by:

- Clinical history and examination
- Level of consciousness (LOC) (Glasgow Coma Scale)
- MiniMental test [standardized for the local population]
• Speech, tongue - twister, repetitive sounds [appropriate to local language]
• Eye movement control (sophisticated ocular motility tests at tertiary medical centres) - pursuit movements (saccadic intrusions), nystagmus, saccades (latency of onset, speed of movement, fluency to be conducted at tertiary centres as part of more sophisticated evaluation), vestibular - ocular movements (fixation is maintained while head is passively moved), optico-kinetic nystagmus (rotating drum)
• Hearing a whispered voice at 2 feet [0.6m], tuning fork
• Hallpike-Dix manoeuvre (central lesions characterized as non-fatiguing as opposed to labyrinthine pathology)
• Postural maintenance, postural tremor, finger nose test, misjudging of distance (dysmetria)
• Repetitive movements (tapping, dysdiadochokinesis, pinch grip, heel-to-shin test, tapping foot)
• Gait (unsteady, tandem walking)
• Postural reflexes – capacity to regain standing posture when pushed

The meeting also felt that it was important to keep assessment simple, using a validated examination e.g. modified Adelaide scale (obey command, localize to pain, verbal, eye response), or Blantyre Coma Scale (motor and verbal responses to pain, ability to look). It was admitted, however, that these examinations, given the extent of the lesions, might not be sufficiently detailed or sensitive enough.

Given the large numbers of patients who have had clinical and auditory assessment following treatment with this group of drugs, without any evidence of neurotoxicity, the group focused on what additional studies were necessary to exclude neurotoxicity in man.

The principles for assessing the potential neurotoxicity of the group of drugs included:

• The significant role of a thorough clinical history (e.g. coordination and balance disorders can be readily detected by a functional history).
• There is a need for a detailed neurological examination, as the damage in animal studies occurs in small areas of brainstem, and limited brainstem and cerebellar dysfunction might otherwise be missed
• This effect is not idiosyncratic, but dose-related, so a detailed assessment should be focused on those patients most at risk (believed to be those exposed repeatedly or at high doses to lipophilic compounds, such as AE, AM, DQHS).
• As neurological abnormalities occur anyway after severe malaria, it might be best to study uncomplicated cases, although Prof. Molyneux pointed out that the risk of toxicity might be greater in severe malaria, as infected red blood cells concentrate DHQS 300-fold, and Prof. Milhous raised the possibility of a parasite burden effect.
• Timing of examination during clinical studies will be important as the effect seen in animal experiments has usually been apparent between 3 – 7 days after dosing. Although neuronal necrosis is permanent, patients may compensate for neurological deficit over time. Auditory and vestibular assessment are considered especially necessary given the site of the animal lesions.
• Higher cortical functions should be assessed, as diffuse or minor abnormalities may lead to abnormality in higher function.
• Prof. Folb commented that new animal studies would be of little investigative value at this stage, as they are removed from clinical experience and a pharmacokinetically comparable model was not available.
In terms of detailed assessment at specialist centres, the following investigations were mentioned:

- Enolase in the CSF, which is a specific marker of neuronal necrosis, might be assayed if CSF were available. The ethics and feasibility of doing lumbar punctures in cases of uncomplicated malaria were questioned.
- The quantitative caloric test with monitoring by ocular vestibulography might be assessed.
- MRI (magnetic resonance imaging) to look at size of inferior olive; PET (positron emission tomography) scanning (glucose utilization), MIS, MRS (magnetic resonance spectroscopy) also mentioned. A specialist MRI radiologist should be consulted regarding the potential usefulness of special radiography, and to define level of resolution, whether enhancement is necessary and whether various MRI signal enhancement protocols might be helpful. These would require a specific objective; in brainstem nuclei investigations, the sensitivity of these techniques is not likely to be sufficient to identify the apparently small lesions in the brainstem.

It was suggested that such specialist investigations might first be validated in animals, as the inferior olive nucleus might be too small for the effects of limited chromatolysis and sparse single cell necrosis to be seen. If no abnormality can be detected in animals shown to have the most severe histopathological changes, then the techniques are unlikely to be helpful in patients with no or minor neurological defects.

From a drug regulatory perspective it was felt that:

- Drug surveillance should be continued throughout future studies, using only simple bedside tests (with the possibility of video recording of eye movements in a subgroup of patients for subsequent, more detailed assessment)
- Specialized detailed studies (MRI, enolase assay) may be necessary to increase confidence when the drugs are to be widely deployed, provided that they have been shown to be capable of giving sufficient sensitivity.

**Q: What is the minimum, therapeutic plasma drug concentration for this group?**

Prof. White stated that a recent study indicated that the lowest mean dose of oral artesunate giving maximal effect on parasite clearance was 2 mg/kg. Therefore, given the large inter-patient variability in kinetics, it would be prudent to keep at least initial doses above this (i.e. 4 mg/kg).

**Artesunate Phase IV Field Trials**

The rural setting, age of patients, and danger of generating invalid data should be borne in mind as requirements for surveillance for possible neurotoxicity during Phase IV artesunate field studies. Dr Ribeiro described the Phase 4 Study Design: i.e. rural, village level, randomized placebo-controlled clinical trial with individual/cluster randomisation, clinical diagnosis of malaria plus ‘nil per os’, with all patients referred to hospital for completion of treatment. Examination would occur at baseline, admission, discharge, early and late (6 - 12 months) follow-up. Dr Ribeiro and Dr Yatsu proposed that the following be monitored:

- At village level: level of consciousness (LOC) (alert / obtunded / comatose) could be evaluated by the village health worker by assessment of verbal response and pain localization (call name, yell and pinch).
At hospital level:
- LOC (modified Adelaide or Blantyre Coma scale)
- Mental status (memory)
- Cranial nerves (follow finger in round circle, hearing the rapid rubbing of fingers)
- Motor (raise arm)
- Coordination and balance (walking in straight line)

Limited examination in infants - except for LOC, and questions to mother, such as “Is the child acting the same?”

The group was aware of possible confounding by pre-exposure, and concomitant management although it was assumed that randomization would distribute confounders evenly. Extensive discussion of which methods and investigations were appropriate was concluded by the neurologists agreeing to prepare a consensus recommendation, for inclusion in the Phase 4 Case Record Form (Appendix 1).

Retrospective studies

The following were recommended for re-assessing patients included in earlier (AM / AE) studies:
- Full history
- Full examination
- Psychometric test, appropriate for community
- Video records of eye movements in children aged over 3 years
- Audiometry
- Sound lateralization with click stimuli
- AEP
- Best available scanning [not CT scans as radiation dose not justifiable]

Although this study was considered feasible (in Malawi, Thailand and Viet Nam) it would be important to avoid selection bias which occurs over time if there has been significant loss to follow up, and with compensation of any neurological deficit with time. This would dilute information gleaned.

Prospective Studies

Given the limitations of the above studies prospective investigations in specialised centres were also recommended. In such studies 20 patients might be followed in detail, using similar neurological assessment methodology as in the retrospective studies described above. To look for a class effect, this type of study should look at AM / AE-treated patients and controls.

Information Exchange

Dr Lugt recommended that the group should review the AE file, with the permission of WHO. Dr Gomes reassured the group that WHO/TDR had approached potential neurotoxicity as a class issue, had reviewed the AE file and encouraged exchange of information between all parties involved in the development and use of this class of compounds for the treatment of malaria.

Dr Dayan closed the meeting by summarizing these recommendations and thanking the participants.
LIST OF PARTICIPANTS

Folb, P.I., University of Cape Town, Medical School, Department of Pharmacology, K45 Old Main Building, Observatory (K/C), 7925 South Africa
Tel: 27 21 47 16 18; Fax: 27 21 448 61 81; e-mail: pfolb@uctgsh1.uct.ac.za

Barnes, K., University of Cape Town Medical School, Dept of Pharmacology, Observatory 7925, Cape Town, South Africa
Tel: 0027 21 406; fax: 0027 21 448 61 81; email: kbarnes@uctgsh1.uct.ac.za

Navaratnam, V., Director, Centre for Drug Research, Universiti Sains Malaysia, Minden Campus, Penang, Malaysia
Tel: 604 6577 888/6568 3444; Fax: 604 6577 957; email: Nava@usm.my

Molyneux, M.E., Wellcome Trust Centre, College of Medicine, University of Malawi, Box 30096, Blantyre 3, Malawi and School of Tropical Medicine, University of Liverpool, UK.
Tel: 265 6301 128 or 82 1238; Fax: 265 6301 29; email: mmolyneux@malawi.net

Ribeiro, I., 13, Prince Edward Mansions, Moscow Road, London, W2, UK
Tel: 0044 171 221 3447; Fax: 0044 171 221 3447; email: iribeiro@aol.com

White, N., Faculty of Tropical Medicine, Mahidol University, 420/6 Rajivithi Road, Bangkok 10400, Thailand
Tel: 00662 2460 832; Fax: 00662 246 7795; email: Prof. Nicholas White, tmnjw@mucc.mahidol.ac.th

Brewer, T., USA Army Medical Component, Armed Force Research Institute of Medical Sciences, APO Area, Pacific 96546, 315/6 Rajivithi Road, Bangkok 10400, Thailand
Tel: 00662 245 90 56; Fax: 00662 247 6030/245 72 84; email: brewer@wrairemhl.army.mil
(UNABLE TO ATTEND)

Binka, F., Navrongo Health Research Centre, P.O. Box 114, Navrongo Upper East Region, Ghana
Tel: 072 3425; Tel/Fax: 233 21 401550; email: fbinka@africaonline.com.gh

Dayan, A., Department of Toxicology, St Bartholomew’s and the Royal London School of Medicine, Charterhouse Square, London EC1M 6BQ, UK
Tel: 171 982 6123; Fax: 171 982 6135; email: A.D.Dayan@mds.qmw.ac.uk

Genovese, R., Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington DC, 20307-5100, USA
Tel: 202 782 3067; Fax: 202 782 6910; email: dr_raymond_genovese@WRSMTCP-CCMAIL.ARMY.MIL or genovese@wrairemhl.army.mil
(UNABLE TO ATTEND)

Hien, Tran Tinh, Centre for Tropical Diseases, Cho Quan Hospital, 190 Ben Ham Tu, District 5, Ho Chi Minh City, Viet Nam
Tel: 84 8 8353804; Fax: 84 8 8353943/8353904

Lugt, Ch. B., ARTECEF BV, Straatweg 2, 3600 AA Maarssen, The Netherlands
Tel: 0031 30 245 22 67; Fax: 0031 30 245 22 66

Milhous, W.K., Director, Experimental Therapeutics, Walter Reed Army Institute of Research, Washington DC, 20307-5100, USA
Tel: 303 295 77 88; Fax: 202 576 31 14; email: col-wil-milhous@wrsmtcp-ccmail.army.mil

Moneton, P., Sanofi Winthrop, 82, Avenue Raspail, 94255 Gentilly Cedex, France
Tel: 0033 1 41 24 65 11; Fax: 33 1 41 24 78 44
Phuapradit, P., Mahidol University, Department of Medicine, Division of Neurology, Ramathibodi Hospital, Rama VI road, Bangkok 10400, Thailand
Fax: 00662 246 2123

Schuster, B., Walter Reed Army Institute of Research, Drug Development, Washington DC 20307-5100, USA
Fax: 001 202 782 3114; email: col_brian_schuster@wrsntp-cemail.army.mil
(UNABLE TO ATTEND)

Skelton-Stroud, Novartis Pharma AG, K. 135.1.76 4002 Basel, Switzerland
Tel: 41 61 696 8558; Fax 41 61 696 6992, email: paul.skelton-stroud@pharma.novartis.com
(UNABLE TO ATTEND)

Thomas, P.K., Royal and University College Medical School, University of London, Department of Clinical Neurosciences, Rowland Hill Street, London NW3 2PF, UK
Tel: 171 794 0500; Fax: 171 431 1577; email: janat@rfhsm.ac.uk

ter Kuile, F., CDC Kemri, P.O. Box 1578, Kisumu, Kenya
Tel: 254 35 22902/59/81; Fax: 254 35 22981; email: feiko@kenya.cdc.gov

Weerasuriya, K., University of Colombo, Faculty of Medicine, Department of Pharmacology, P.O. Box 271, Kynsey Road, Colombo 8, Sri Lanka
Tel: 94 1 69 5230; Fax: 941 57 3170; email: kw_twcp@slt.lk

Yatsu, F., Department of Neurology, University of Texas, Houston Medical School, Houston, TX 77030, USA
Tel: 001 713 500 7100; Fax: 001 713 500 7019; email: fyatsu@heart.med.uth.tmc.edu

**WHO Secretariat:**

Dr A. Bosman, CTD/MAL; email: BOSMANA@WHO.CH

Dr C. Delacolette, CTD/MAL; email: DELACOLETTEC@WHO.CH

Dr D. Broun, CTD; email: BROUND@WHO.CH

Dr M. Gomes, TDR/TDF Fax: 41 22 791 4774; email: GOMESM@WHO.CH

Dr W. Gutteridge, TDR/TDP Fax: 41 22 791 4854; email: GUTTERIDGEW@WHO.CH

Dr J. Lazdins, TDR/OCT, email: LAZDINSJ@WHO.CH

Dr K. Mendis, TDR; email: MENDISK@WHO.CH

Dr P. Olliaro, TDR/TDF Fax: 41 22 791 4774; email: OLLIAROP@WHO.CH
## DISCHARGE FORM

### Appendix 1

**Date of discharge** ......./...../.....  **Study adm. Time** ......./...../.....

**Dd/mm/yy** e.g. 13:47

**Date of admission** ......./...../.....  **Outcome**

- [ ] Survived
- [ ] Died

**Treatment to go home**

- [ ] Off medications
- [ ] Quinine
- [ ] Sulphadoxine-pyrimethamine
- [ ] Iron
- [ ] Folate
- [ ] Paracetamol

---

Does the patient have any new problems with the following?

**Feeding**

- [ ] Yes
- [ ] No
- [ ] NK

**Walking**

- [ ] Yes
- [ ] No
- [ ] NK

**Talking**

- [ ] Yes
- [ ] No
- [ ] NK

**Sitting**

- [ ] Yes
- [ ] No
- [ ] NK

**Sight**

- [ ] Yes
- [ ] No
- [ ] NK

**Hearing**

- [ ] Yes
- [ ] No
- [ ] NK

**Playing**

- [ ] Yes
- [ ] No
- [ ] NK

**Balance**

- [ ] Yes
- [ ] No
- [ ] NK

**Behaviour**

- [ ] Yes
- [ ] No
- [ ] NK

---

If answered "yes" to any of the above questions, please specify ............................................................

............................................................

............................................................

---

**Pulse** .........  **SBP** .........  **Weight at discharge** .........kg

**Temperature** .........

**axillary**

---

Response to painful stimulus (Blantyre Coma Score) Best=5

**Eye movements**

- [ ] 1 Not directed
- [ ] 2 Directed

**Verbal response**

- [ ] 0 None
- [ ] 1 Moan or inappropriate cry
- [ ] 2 Appropriate cry

**Best motor response**

- [ ] 0 Non-specific or absent response
- [ ] 1 Withdraws limb from pain
- [ ] 2 Localises painful stimulus

---

Ability to follow a circle (with both eyes)

- [ ] Normal
- [ ] Abnormal
- [ ] Too young to perform task
- [ ] Uncooperative with exam

**Nystagmus**

- [ ] Present
- [ ] Absent
- [ ] Too young to perform task
- [ ] Uncooperative with exam

Ability to hear the rapid rubbing of fingers (within 2 in or 5 cm from both years)

- [ ] Normal
- [ ] Abnormal
- [ ] Too young to perform task
- [ ] Uncooperative with exam

---

If abnormal, please specify ............................................................

............................................................

............................................................
<table>
<thead>
<tr>
<th>Speech</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Not yet speaking</th>
<th>Uncooperative with exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>If abnormal, please specify...</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ability to raise both arms</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Too young to perform task</th>
<th>Uncooperative with exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the child walk steadily?</td>
<td>Yes</td>
<td>No</td>
<td>Too young to perform task</td>
<td>Uncooperative with exam</td>
</tr>
<tr>
<td>Heel-toe walking</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Too young to perform task</td>
<td>Uncooperative with exam</td>
</tr>
<tr>
<td>If abnormal, please specify...</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Romberg</th>
<th>Present</th>
<th>Absent</th>
<th>Too young to perform task</th>
<th>Uncooperative with exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picking tablets</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Too young to perform task</td>
<td>Uncooperative with exam</td>
</tr>
<tr>
<td>Pencil touching</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Too young to perform task</td>
<td>Uncooperative with exam</td>
</tr>
<tr>
<td>Rapid hand tapping</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Too young to perform task</td>
<td>Uncooperative with exam</td>
</tr>
<tr>
<td>Drawing a spiral</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Too young to perform task</td>
<td>Uncooperative with exam</td>
</tr>
<tr>
<td>If abnormal, please specify...</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Fever clearance time (=time in hours till axillary temperature falls below 37°C and remains below 37°C for 2 subsequent 4 hourly readings) | .......hrs |
| Parasite clearance time (=time in hours till the first of 2 consecutive negative blood films) | .......hrs |

When did the patient become able to:

| Eat at .......... (e.g.13:47) on (date dd/mm/yy) ........../...... |
| Drink at ..........(e.g.13:47) on (date dd/mm/yy) ........../...... |

Follow-up arranged? Yes | No | Time of death: ....... Date of death: ......./......

Date of follow-up: ......./......
REFERENCES:

1 A D Dayan “Neurotoxicity and Artemisinin Compounds. Do the observations in animals justify limitation in clinical use?” Paper presented at a Conference convened by the International Laveran Association, Annecy France 19-22 April 1998


9 Price RN et al. “Treatment of acute falciparum malaria with artemisinin derivatives: an analysis of adverse effects from prospective studies in 3645 patients” Submitted to publication.
