Meeting of the working group on monitoring of drug efficacy in large-scale treatment programmes for onchocerciasis control

Geneva, 3 to 5 March 2008
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1. Introduction

Following the WHO-World Bank meeting on "Monitoring of Drug Efficacy in Large-Scale Treatment Programmes for Human Helminthiasis" held at the World Bank Headquarters in Washington DC, 31 October - 2 November 2007, the decision was taken to establish Working groups to create standard operating procedures for surveillance tools for the different drug/parasite, as well as clear definitions for the early detection of drug resistance.

The Working group on monitoring of drug efficacy in large-Scale treatment programmes for onchocerciasis control, coordinated by Dr Uche V. Amazigo, Director of APOC, held its meeting, co-sponsored by APOC, TDR and NTD/Geneva in Geneva, from 3 to 5 March 2008. The agenda of the meeting, as well as the list of participants, are presented as annexes 1 and 2.

2. Opening

The opening ceremony was held under the auspices of Drs Lorenzo Savioli, Director of the WHO/HQ’s department on Neglected Tropical Diseases, Dr Robert Ridley, Director of WHO/World Bank/UNICEF/UNDP Special Programme for Tropical Disease Research (TDR) and Dr Uche V. Amazigo, Director of the African Programme for Onchocerciasis Control (APOC).

In their opening remarks, they welcomed participants and stressed the importance of the meeting with regards to the subject to be discussed which is vital for control programmes. Dr Savioli laid emphasis on the attention currently being given to research on NTDs as well as their control. He also pointed out the leading role the onchocerciasis control programmes played 21 years ago by initiating this long-term partnership with a pharmaceutical company through the donation of ivermectin for as long as needed. The Director of TDR informed participants of the new research strategies/directions of TDR and invited them to visit their web site for detailed information. In this new context, the importance of the interface between TDR and APOC as well as TDR and NTD was emphasized by Dr Ridley who also mentioned the need for a better link between the development and manufacture of research products. An intergovernmental working group has been established on public health, intellectual property and innovation. Dr Amazigo, who thanked participants for accepting her invitation, welcomed the collaboration among APOC, TDR, NTD department and international scientists as an important means of defining and addressing key issues as the one on ivermectin efficacy. She expressed the hope that the expected outcome would be fully achieved to the benefit of control programmes.
Professor Mamoun Homeida, Chair of the meeting, indicated that resistance is a general concern, particularly in this precarious situation with the limited number of drugs available for the control of NTDs (Praziquantel as the main drug for schistosomiasis; ivermectin as the only drug for onchocerciasis). He hoped that research would help us overcome this situation. He then asked participants to introduce themselves before proceeding to the next agenda item.

2.1. Adoption of agenda

The draft agenda presented as annexe 1 was adopted.

2.2. Expected outcome

Dr Laurent Yaméogo made a recall for the benefit of participants relative to the background of the Meeting of the Working group (WG) on monitoring of ivermectin efficacy in large-Scale treatment programmes for onchocerciasis control, which is the above-mentioned Washington meeting.

The objectives of this meeting were:

i. to review the current status of drug efficacy for the different drug-parasite combinations (in veterinary medicine and human public health);
ii. to learn from drug efficacy surveillance in other fields (HIV, TB, malaria, and veterinary parasitology);
iii. to determine how anthelminthic efficacy in humans could be monitored;
iv. to evaluate the adequacy of monitoring tools;
v. to discuss what actions could be taken if efficacy was reduced; and
vi. to discuss what cut-off levels could be set for action.

One of the decisions taken by the meeting was to establish disease-specific working groups to create standard operating procedures for surveillance tools for the different drug/parasite, as well as clear definitions for the early detection of drug resistance. These should lead to the establishment of draft guidelines for anthelminthic drug efficacy monitoring by mid-2008. The expected outcome of the meeting of the Working group on monitoring ivermectin efficacy for onchocerciasis control was therefore to:

a) Formulate clear definitions of drug resistance;
b) Prepare guidelines for monitoring ivermectin efficacy for onchocerciasis control;
c) Suggest new sensitive tools for early detection of drug resistance and define procedures for developing these tools.

As part of the discussions under this agenda item, Dr Dirk Engels (Coordinator, PCT WHO/HQ), updated the meeting on what has been happening in other working groups since the Washington meeting. Among the 5 Working groups proposed in Washington (soil-transmitted helminthiasis (STH), schistosomiasis, onchocerciasis, Lymphatic Filariasis and one on pharmacology issues, the TAG recommended that LF would not have its own meeting, but their experts would participate in the WG on STH and onchocerciasis, because they use the same drugs. The onchocerciasis WG was the first to meet but the STH/benzimidazole have done some preparatory work and have established a workplan. They will meet in April in Gent. A joint meeting of WGs is planned before the end of the year to pool the recommendations together. Common issues in the different working groups should be:
- Diagnostics;
- Definitions of potential resistance (threshold with a diagnostic methods, combined with exclusion of operational or mathematical confounding factors);
- Laboratory confirmation of resistance, ideally by molecular tools (are the tools available?);
- Research agenda for developing the new tools.

3. Evidence for ivermectin resistance

3.1. Summary of published reports

Dr. Awadzi reviewed the evidence for ivermectin resistance in clinical reports. Four papers presented relevant data, one from Sudan and 3 from Ghana:


This study investigated displaced people, who came from heavily endemic areas in southern Sudan to Kartoum, where they were no longer exposed to infection. They were treated with ivermectin, but pruritus often returned earlier than assumed. The impact of ivermectin on skin mf load was compared in 47 subjects with poor response (in terms of pruritus) and 12 normal responders. In poor responders, the skin mf density reached 68.4% of pretreatment loads at 4-6 months against 10.1% in normal responders. The cellular immune responses to *O. volvulus* antigen-specific cell transformation of blood lymphocytes (expressed as the stimulation index SI (counts per minute of stimulated cultures divided by those of unstimulated cultures) were impaired in the low responders compared to controls. Role of poor microfilarial or adult worm responses to be determined.


The objective of the study was to investigate the causes of persistent microfilaridermias, despite multiple treatments with ivermectin, in two onchocerciasis-endemic foci in Ghana. Three groups were compared:

- Suboptimal responder:
  - Field definition >= 10 mf/snpl in spite of repeated treatments
  - Hospital definition >0 mf/mg at iliac crests and calves
- Responder: zero mf at all time points
- Ivermectin-naïve: no previous treatment with ivermectin (Tordzi basin).
The effect of ivermectin on mf was considered good when the reduction in skin mf count on day 8 was >60% and when L3 larvae were absent in flies, which were fed on these individuals 8 days after treatment. The response to adult worms was considered to be good when the embryogrames were inactive (no multicellular stages) and when the skin mf count was still <= 6% of the initial count on day 90 and < 40% at day 365.

The suboptimal response was unlikely to be caused by pill and patient factors; parasite factors were identified as the main explanation. The impact of treatment on mf was generally good, but the effect on adult worms was often less than good. The number of worms genotyped was too low to draw conclusions about changes in genetics.


This was a follow-up study to the previous one, aiming to confirm previous observations and to test whether it would be justified to use suramin in these patients. They relocated the same patients as in the earlier study. Many of the suboptimal responders had new nodules with active embryogrames; one other individual had no nodules but very high skin mf loads indicating the presence of productive female worms. The intra-uterine stretched mf were mostly degenerated and suggests that, although ivermectin failed to suppress embryogenesis, the ability to sequestrate mf in utero was preserved. Suramin treatment is justified and is likely to be well tolerated due to low skin mf in most patients.


The objective was to investigate *O. volvulus* endemicity, the field efficacy of ivermectin, and the effect of ivermectin on adult female worm reproduction. A two-phase study was therefore performed in 4 districts in Ghana (Kintampo in the Lower Black Volta river basin; Atebubu and Nkoranza in the Pru river basin; Gonja East in the Daka river basin):  
- Phase 1: after protocol approval and informed consent procedures, 2501 individuals were randomly selected from 19 onchocerciasis endemic communities that had received 6-18 rounds of ivermectin and from one ivermectin naïve community. Subjects were skin snipped (2 snips) 7 days before and 30 days after treatment with 150 µg/kg of ivermectin (ssnips +ves only);  
- Phase 2: skin snips were taken from 342 individuals, who were microfilaria positive at pretreatment assessment, on days 90 and 180 after treatment, to identify the effects of ivermectin on female worm fertility, assessed by microfilaria repopulation.

*Results phase I*: The mf prevalence was 19% in the 2501 individuals (range in mf prevalence was 2.2-51.8%; range in CMFL: 0.06 – 2.85 mf/snip in different communities). Despite treatment, the mf prevalence doubled between 2000 and 2005 in 2 communities. Mf
assessment 30 days after ivermectin treatment showed 100% clearance of mf in more than
99% of people.

Results phase II: At day 90 after treatment, 4/10 communities had significant mf repopulation,
from 7.1% to 21.1% of pretreatment counts, rising to 53.9% by day 180.

It was concluded that ivermectin remains a potent microfilaricide, but that
repopulation rates are unusually high. This could indicate emerging resistance. Because drug
resistance has a genetic basis, monitoring of genetic markers associated with ivermectin
selection and resistance should be undertaken.

In summary, the three studies in Ghana, which were all done in the same areas,
distinguished between the impact of treatment on mf and the impact on female adult worms.
They all showed that ivermectin remains a potent microfilaricidal, but that some worms
continue producing mf. The 3 studies covered the same problematic areas.

During the discussions, it appeared that some problematic aspects complicate the
interpretation of the Ghana-studies results:
- Some treatment-naïve people also had a poor response.
- Continuing transmission in recent years might have introduced confounding factors.
- Available data from genetic studies might support the conclusion of resistance, but
  that data is also problematic and do not provide definitive evidence of resistance.

3.2. Follow-up studies in Ghana

Dr. Hans Remme of TDR presented the results of the coverage study, performed by the
national onchocerciasis control team of Ghana in collaboration with APOC, to clarify the
situation in the problematic area and to investigate whether poor ivermectin treatment
coverage could be an alternative explanation for the high repopulation rate. Detailed surveys
were done in the study areas to collect spatial information on treatment coverage for the
period 1997-2004 for all villages within a 20 km radius and to map regular and irregular
repopulation rates:

- Pru district. All villages in this district had normal repopulation rates. Asubende,
  which is known to be a village with very high prevalence levels of mf and blindness, is
  in the core of the district. All villages had seven rounds of treatment in the period of
  1997-2004 ; those with missing data were also likely to have had seven rounds.
  Therapeutic coverage was more difficult to assess ; coverage levels were moderate
  (45-59%) in some villages in the core areas around Asubende.
- East Gonja: Two villages in this district had rapid repopulation in the Osei study. The
  single control village with no previous treatment was also located in this district. Data
  showed very poor geographic coverage : in many of the villages there has been no
  treatment or only two treatment rounds. Infection could therefore be introduced from
  one village to another.
- Kintampo district was the most difficult. There were many hamlets in the study area,
  and it was not sure whether they were treated. In one part of the district, 7 treatment
  rounds were provided, but in other parts there was zero or only few treatment rounds.
  But little information on therapeutical coverage was available about villages in the
  direct surroundings of the study villages. Reported therapeutical coverage rates were
  very high (and seem unrealistic, given the large proportion of non-eligibles in
populations). The reported coverage rates in the study villages with high repopulation rates were not high. One village had coverage levels varying from 0-50% in the period of interest (average ~30%) ; the other village had better coverage, but with a dip in 2001-2002, i.e. immediately preceding the Lancet study. Close to study villages there were some hamlets / villages with very few treatments.

In summary, Pru had good geographic coverage, but low therapeutic coverage. Normal repopulation rates were seen in this village. The number of viable female onchocercal worms per nodule was low. East Gonja and Kintampo had poor geographic coverage and low to moderate therapeutic coverage. The villages with fast repopulation rates were in this area. The number of viable female onchocercal worms per nodule was somewhat higher than in the Pru area.

The patterns were consistent with the alternative hypothesis that ongoing transmission contributes to higher repopulation rates. It is important to note that the observations from Ghana have not been replicated elsewhere. Mali and Senegal, which have many years experience with mass treatment are now close to eliminating the disease using ivermectin alone.

The complete collaboration provided by Ghana MoH (Johnny Gyapong and his team) and Noguchi Memorial Institute for Medical Research (Daniel Boakye), the hard work of the consultants as well as the APOC staff was acknowledged and appreciated by Dr Amazigo who thanked Dr Remme for his extremely valuable guidance in analyzing this data.

- The Working group members noted the discrepancies between this data and that in the Osei-Atweneboana et. al. paper published in the Lancet. These discrepancies need to be sorted out (sources of information, definition of treatment coverage, denominator) as recent entomological data (2006-2007) reveal that infectivity rates are acceptable in the Pru area while in the North and the South, the infectivity rates are higher than the threshold 0.5%. This underlines the difficulties in getting reliable coverage data. Many questions remain unanswered about coverage and transmission. Further field studies may not be helpful in the clarification being looked for. Repopulation rates depend on the number of treatments provided, coverage, and biting rates. The underlying factor is the number of female adult worms that resume mf production after treatment. The ONCHOSIM model might be a useful tool to analyze the data in more detail and test whether the alternative hypothesis brought forward could indeed explain the observations. In the Lancet paper, very few young worms were found in the nodules, which is quite difficult to understand in this context. There is no reason to assume that young worms are missed by nodulectomy.

- There is lack of clarity about the impact of worm-age on mf productivity: some data suggests that middle-aged worms produce most mf, followed by older worms; youngest worms produce less mf. However, the definition of young, middle-age and old worms is not entirely clear. Moreover, it is possible that these worms respond differently to treatment.

- Confounding factors seem to be the usual culprits. Recurring : getting good information about the confounders is particularly difficult. Are there surrogates that sum up all these factors? Perhaps transmission potential is the most important one.

- One river basin in Togo also performed poorly and there was the fear that parasites might have gotten resistant. However, field data showed that coverage and compliance was poor. Following reinforced control activities of the programme to improve
coverage and compliance, it has resulted in clearing the infection. This underlines the importance of this factor.
- Little information from the Americas, where very intensive treatment schedules are in place. They have not found resistance.

In conclusion, from the results of the different studies conducted in Ghana and discussed during the meeting, coverage and continuing transmission cannot be excluded as alternative explanation for the high repopulation rates. The use of retrospective information while knowing the difficulties the control programme has in reporting coverage does not facilitate the understanding of the situation. In any further study on drug-resistance, it is recommended to have sound baseline data on transmission, coverage and infection in human. The ideal study should therefore be:
  o Prospective instead of retrospective;
  o Performed in treatment naïve areas so that we can measure the baseline situation;
  o Performed in different endemic situations. Repopulation rates are not always the same; it is not safe to use a single reference line. They depend on the number of treatments provided, coverage and biting rate. ONCHOSIM can be used to examine repopulation rates in different situations.

4. Definitions

4.1. Definition of ivermectin efficacy

Conceptual definition of ivermectin efficacy on mf
A standard dose of 150 µg/kg has the normal efficacy against mf, namely it causes nearly complete clearance of mf in the skin and eye, improvement in skin and ocular lesions, and/or a Mazotti reaction.

Conceptual definition of ivermectin efficacy on adult worm
A normal efficacy against the adult worm is indicated by failure of mf to return to the skin or eye, suppression of embryogenesis; the impact on worm vitality remains uncertain

Operational definition of a good response at individual level:
Obtained by analyzing time trends in mf count after ivermectin treatment in 88 patients.

Operational definition of poor efficacy in one or more of the parameters (at population level):
Annual treatment no longer effective to control onchocerciasis as a public health problem: CMFL increases or >5 mf/skin snip despite repeated treatment with good treatment coverage (100% geographic coverage; >= 65% therapeutic coverage).

4.2. Definition of ivermectin resistance

Conceptual definition of resistance at molecular level
The worm population has a different genetic make-up than non-treated populations, which results in a reduction in ivermectin efficacy.
**Operational definition of resistance at molecular level**
- Where the presence of a resistant genotype predicted accurately the loss efficacy of ivermectin
- At present, we do not know what the resistant genotypes are. Therefore, we cannot give an operational definition for resistance at molecular level.

**Operational definition of potential resistance**
Unexpectedly high mf levels (fall below 95% of ‘normal’ efficacy at 3 months after treatment; numbers to be defined by subgroup of the meeting);

**Clinical consequences of resistance:**
Clinical manifestations are no longer controlled by approved dosages and regimens associated with unresponsive parasites.

**Recommendation:**
We should involve population genetics in the design of the future studies to ensure sampling design is unbiased and free from confounding factors. This concerns both sampling in human population and the parasite life stages considered.

5. **Parasitological monitoring of ivermectin efficacy**

5.1. **Recommendations**

a) Routine surveillance by the Programme will identify pre-treatment skin snip positive subjects, including their mf/snip load

b) Efficacy monitoring will be done in a subgroup of communities under surveillance, selected based on the following criteria

- Meso- or preferably hyper endemic
- identified by routine surveillance as having a prevalence of 10% or more
- treatment history ranging from 5-12 years
- a level of infection different from that expected, based on treatment history (including coverage)
- virgin areas impact of potential recurrence of recurring conflict

C) Efficacy monitoring will be done via skin snips at 3 months post-treatment in all pre-treatment positive subjects who agree and were treated after the snip. The overall timeline for the efficacy monitoring is presented as figure 1.

D) Criteria for interpreting data on efficacy monitoring should take into account:

- reduction from 99% efficacy to 95%
- additional historical information on efficacy as well
- additional information on the percentage of reduction from published guidelines will be provided by Dr Warwick Grant
- An internal group to work this out and advise.
6. Development of new tools for early detection of resistance

6.1. Parasite genotyping and the detection of resistance

Previous research by a TDR Product Development Team identified two sets of markers: candidate genes chosen on the basis that they could mediate a plausible resistance mechanism (in part based on experience with animal parasites), and randomly chosen anonymous genetic markers. There is evidence that some of these markers differ between worms taken from treated and untreated patients, consistent with genetic selection by ivermectin and potentially linked to the non-responder or resistant phenotype. These genetic markers will be the starting point for the development of new tools.

The following recommendations were made for the development of these new tools:

(i) These new tools will be molecular tools. The first step is to reconvene the Product Development Team (PDT), which will meet no later than June 30, 2008, to develop a plan for reactivation of the previous work on genetic markers.
(ii) The PDT should consider how best to resume work on the candidate genes and anonymous markers to permit transfer of this technology to African partners, and should review recent technical developments in the field to determine whether opportunities exist to enhance the value of the earlier work. This review should include, but not be limited to, new techniques for data analysis, high throughput generation of genetic markers and new genotyping methods.
(iii) This plan will include a checklist of desirable criteria for selection of partner laboratories in APOC countries, one (or more) of which will be the reference laboratory and repository for samples, and the centre where genotypic analysis and data storage will be carried out. The call for partners should be made no later than August 2008.
(iv) The June meeting of the PDT will include representatives from APOC to ensure direct APOC participation in the development of the plan, and coordination and communication of the proposed work with APOC. The meeting may also include additional participants, whose expertise is required for proper formulation of the plan.

6.2. Collection and storage of parasitological material

Source and type of material, collection and preservation

- microfilaria collected during APOC routine surveillance and efficacy monitoring will be the primary source of parasite material for genetic analysis. They will most likely be collected and stored in the field in isopropanol and will be collected at the time of surveillance and efficacy monitoring.
- nodules and/or entomological material will be collected in collaboration with APOC as a follow-up action. The communities will be selected using the same parasitological criteria as those described for selection of communities for
control program follow-up of non-response. Nodules will most likely be collected into (and stored in) liquid nitrogen.
  o Operational decisions on where and from whom to collect nodules and/or entomological materials is delegated to APOC.

**Sample documentation/information**

The PDT will define the information that needs to be provided with each sample to permit proper interpretation of the genetic data.

6.3. **Analysis / genetic evaluations**

Move with the markers that were already identified, but continue to look for new markers. Analysis / genetic evaluation: this section will be prepared by a separate subgroup.

6.4. **Organization**

6.5. **Reference laboratory and sample repository**

*Establishment of a reference laboratory (or laboratories) in Africa*: it is essential that the analysis and storage of parasite material collected by APOC be centred in an African reference laboratory or laboratories (see 2 above), in close collaboration with APOC to ensure coordination between PDT and APOC activities.

*Data repository*: the analysis and central storage of data should be coordinated by a single African laboratory so that all genetic data is held in a single, curated database that is freely accessible.

Consideration of how best to facilitate obtaining appropriate ethical approval for the proposed sample collection and analysis; whether this should be covered through APOC surveillance and monitoring or whether additional ethical clearance for genetic analyses is required.

Consideration should be given on how best to facilitate obtaining appropriate ethical approval for the proposed sample collection and analysis.

6.6. **Network of collaborators and technology transfer**

The PDT should consider establishing desirable criteria for selection of collaborators to resume work on the candidate genes and anonymous markers to permit transfer of this technology to African partners. Partner laboratories should include some in APOC countries.

6.7. **Expertise requirements and budget**

The PDT will on the issue and provide the required elements needed for work in APOC and in developed country partner laboratories.

Concerning funds requirements, strategies should be developed for application to external funding agencies to support and expand activities.

Expertise requirements and budget estimates for work in APOC and in developed country partner laboratories.
Strategy for application to external funding agencies to support and expand activities; initial funding is available through APOC and TDR bipartite agreement but additional funding should be sought.

6.8. General rules for collaboration

Management and oversight of research activities

- The Product Development Team (PDT) in TDR will be responsible for the oversight of research activities for genetic markers. Membership of the current PDT will be revisited for possible inclusion of additional members.
- APOC will provide oversight for surveillance, monitoring of efficacy and monitoring operational research.
- The PDT which composition will be announced by TDR, will oversee the activities;
- Before the August meeting, APOC and TDR will come with clear information on their collaboration;
- The Sub-committee of APOC/TCC will contribute to overseeing the research activities.

Ownership of information

APOC and the countries own the crude data collected by the teams in the field within the framework of the activities of the African Programme for onchocerciasis control. The collaborators of APOC, all those invited to take part in the collection of data need to commit themselves and agree that APOC and the countries own the data collected under the umbrella of APOC.

Management of parasitological material

The laboratories collaborating to the work will share (among themselves) the parasitological material.

Management of information and publications

No paper using the data collected by the team will be published without the agreement of the PDT, APOC and TDR. However, it was stressed that legal advice on ownership of data and publication needs to be sought. Drafts of publications on ivermectin resistance and relevant areas should be done in consultation with parties concerned before submission to a journal.

Surveillance and monitoring data should be published in a coordinated way with papers on technical data emerging from the research on genetic markers. General interest journals and local African journals should be considered first for publication of results.

Any product from the material collected and which has been developed using funds provided by APOC/TDR should not be seen as the property of a single laboratory.
Funding

APOC and TDR will fund the first year or two of the studies for genetic markers while the group generates data that can attract funding by other funding agencies for the subsequent years of work.

A funding strategy needs to be developed which considers application for funding not on an individual researcher / PI basis, but in the context of an APOC/TDR connected researcher network addressing specific control programme needs. Funding sources to be considered are the standard, well-known ones, as well as national African funding sources.

It was stressed during discussions that re-initiation of the PDT research will not lead to a direct, diagnostic test for ivermectin resistance. Validation of these tools, via the proposed research, will lead to a portfolio of indicators of genetic selection on worm populations by ivermectin. If such selection is detected, it should serve as an indicator for detailed parasitological and clinical investigation, rather than it being interpreted as a diagnosis of ivermectin resistance. Thus, the expected output of this research will be a genetic criterion, to be used in combination with surveillance and efficacy monitoring data, for more detailed parasitological and clinical investigation.

7. Closure of meeting

Prof. Homeida, chair of the meeting, Dr Amazigo, Director APOC, Dr Remme, on behalf of Director TDR, and Dr Engels on behalf of Director NTD/Geneva, thanked the participants for coming, despite the change of venue and the difficulties they faced with accommodation in Geneva. They expressed also their satisfaction for the frank and fruitful discussions which led to the clear and helpful outcome of the meeting. After wishing all participants coming from outside Geneva a safe journey, Professor Homeida declared the meeting closed.
## Annexe 1

### Monitoring Ivermectin Efficacy in Onchocerciasis Control

**Draft agenda (Rev.2)**  
Chairman: Professor M. Homeida

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<td>Opening</td>
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<td>Evidence for ivermectin resistance</td>
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<td>o Summary of published reports</td>
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<td>o Follow-up studies in Ghana and other data from Togo</td>
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<td>3. Definitions</td>
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<td>a. Definition of ivermectin efficacy (pharmacological/clinical/operational)</td>
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<td>b. Definition of ivermectin resistance (molecular/pharmacological/clinical/operational)</td>
<td>Grant</td>
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<td>4. Parasitological monitoring of ivermectin efficacy</td>
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<td>a. Proposed two-step process for monitoring ivermectin impact and efficacy</td>
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<td>i. Overall process for monitoring impact and efficacy</td>
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|        | ii. Inclusion criteria for areas  
|        |   . Pre-control endemicity level  
|        |   . Duration of treatment / other control  
|        |   . Treatment coverage (spatial, temporal) |              |
|        | iii. Inclusion criteria for individuals / sample sizes |              |
|        | iv. Parasitological examination methodology |              |
| **Tuesday** |      |              |
| 9:00   | Item 4 continued          |              |
| 11:00  | 5. Development of new tools for early detection of resistance | Tait (discussion leader) | Grant / Abiose |
|        | a. Collection and storage of parasitological material |              |
|        | i. Source and type of material |              |
|        | ii. Collection             |              |
|        | iii. Preservation          |              |
|        | iv. Sample documentation/ information |              |
b. Analysis / genetic evaluations

c. Organization
   i. Reference laboratory & sample repository
   ii. Network of collaborators & technology transfer
   iii. Overall data management
   iv. Collaboration with disease control/APOC

d. Expertise requirements and budget estimate

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<td>9:00</td>
<td>e. General rules for the collaboration</td>
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<td>i. Management and oversight of research activities</td>
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<td>v. Funding</td>
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<td>11:00</td>
<td>6. Conclusions of the meeting and draft guidelines</td>
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Annexe 2.

Provisional List of Participants
of the meeting of the working group on monitoring
of drug efficacy in large-scale treatment programmes
for onchocerciasis control

Geneva, 3 to 5 March 2008

EXPERTS

1. Prof. Andrew Tait, Professor of Veterinary Parasitology, United Kingdom -
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