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Upcoming AMANET Workshops:

Clinical Data Management
March 2006

Management and Leadership
July 2006

MIM Secretariat coming to Africa

Charles Wanga

From January 2006, AMANET will host the Multilateral Initiative on Malaria (MIM) Secretariat for the next five years. Speaking recently at the Fourth MIM Pan African Malaria Conference held from 13-18 November 2005 in Yaoundé Cameroon, Professor Wen Kilama, AMANET Managing Trustee, said:

"The transfer of MIM Secretariat to Tanzania is an enormous opportunity. This move is an investment in the future of African scientists and indeed, the future of the African continent itself."

Africa continues to bear the brunt of the malaria burden worldwide. Of the more than a million people dying of malaria every year, more than 80 percent are African children under the age of five. The disease, which has been described by some as "Africa's silent tsunami" claims more than 3,000 lives every day in sub-Saharan Africa alone.



Dr. Andreas Heddini, the outgoing MIM Secretariat Coordinator

"While the work of scientists from outside Africa continues to be critical, the fact remains that African malaria researchers need to be involved in parallel if we are going to successfully implement new research findings and begin to reverse the situation in malaria endemic countries," said Andreas Heddini, the outgoing secretariat coordinator for MIM.

The Multilateral Initiative on Malaria (MIM) is a global alliance dedicated to building a sustainable malaria research infrastructure in Africa. Launched in Dakar, Senegal in 1997, MIM is an international alliance of organizations and individuals seeking to maximize the impact of scientific research against malaria in Africa to ensure that research findings yield practical health benefits. The MIM Secretariat was previously hosted for 3-year terms by the Wellcome Trust (UK) and the Fogarty International Center at the National Institutes of Health (US). In 2003, the Secretariat moved to Stockholm, Sweden, where it is hosted by the Karolinska Institute and Stockholm University.

MIM moving to AMANET will be the first time

the Secretariat is hosted on African soil. "While at AMANET, the Secretariat will build on the achievements made so far by its predecessors" added Prof Kilama.



Professor Wen Kilama, AMANET Managing Trustee

MIM is calling for new, innovative and practical ways of improving research training in Africa. Among ideas being nourished is the initiative that would focus on competitively awarded long-term grants that would be dedicated to developing new "centres of excellence" in malaria endemic areas of Africa. These centres would serve as hubs for training new scientists and assembling interdisciplinary teams for conducting malaria research. In addition, an African malaria research and control forum will be established to translate malaria research results into action which will be coupled with renewed advocacy to promote malaria awareness to the general public and among policy makers. Decision makers need to be targeted for political goodwill and increased African investments in malaria research and control.

The Fourth MIM Pan-African Malaria Conference held in Yaoundé, November 2005 brought together scientists, policymakers, African ministers, health care workers, the media, community members, and other stakeholders under one roof to review efforts to build Africa's malaria research capacity, empower afflicted communities, battle complacency and address the many barriers that are keeping effective malaria prevention and treatment from reaching the most vulnerable.

AMANET contributed to this meeting by facilitating the attendance of over 30 young African scientists and researchers. In addition, AMANET moved two of its end of year statutory meetings to Yaoundé just before and during the MIM Conference making a total of over 50 participants sponsored by AMANET.

The coming of MIM Secretariat to Africa is a call to all Africans to join hands with AMANET and make the MIM alliance realise its goals.

Initiation of Capacity Strengthening and Site Development Projects in 2005

Roma Chilengi

During 2004, AMANET sent out a call for African led malaria research institutions to apply for capacity strengthening grants to enable them build up capacity to be able to undertake malaria vaccine trials. A stringent, but transparent evaluation criterion was pre-set according to standard operating procedures. Out of the 12 applying institutions the Tropical Diseases Research Centre (TDRC), Ndola, Zambia and the National Institute for Medical Research (NIMR), Tanga Centre, Tanzania emerged as the two selected Centres. Thus a grant amounting to €50,000 each was awarded for undertaking relevant infrastructural improvements, train staff at various professional levels, constitute a malaria vaccine trials team and fully characterise their field testing sites.

This is a report of the initiation visits undertaken by AMANET staff as sponsors to officially launch the project, which took place on the days 9-11 August for TDRC and 23-25 August for NIMR.

Opening Ceremonies

At both centres the official ceremony was held at the centre facilities.

Welcoming remarks

The meetings were attended by Ministry of Health officials, Institutional Directors and staff members. Both programmes began with welcoming remarks by the Directors of the institutions (TDRC, Dr. Emmanuel Kafwembe and NIMR, Dr. Martha Lemnge).

The speeches generally gave the background to the Centres' establishment, the historical development, activities undertaken, success and difficulties faced. The AMANET grant was deemed appropriate for the institutions as its programme activities

were all in line with the mandate of the Centres and came at a timely point.

Dr. Ben Chirwa, Director General of the Central Board of Health in Zambia and Mr. Malelemba, official from the Ministry of Health in Tanzania, gave the official welcoming speeches. Both

authorities pledged support to the grantees and appreciated the role that AMANET is taking in promoting malaria research in Africa.

Malaria back ground

The details of the current malaria situation in both countries were presented. An overview of the malaria situation in Zambia was presented in a talk by Dr. Naawa Siplanyambe, the Coordinator for the national malaria control programme. She presented the current malaria situation in the country and provided updates on the efforts being implemented for control including the new treatment policy change, sentinel monitoring of *in vivo* resistance, insecticide treated nets and residual indoor spraying programmes.

Dr. Julius Massaga from the NIMR Headquarters represented the Director General, who could not attend due to other pressing responsibilities. He gave a comprehensive talk about the malaria situation in Tanzania starting from a historical perspective to the current state of affairs highlighting the different strategies for control that have been adopted including insecticide treated bed nets, residual indoor spraying, intermittent presumptive treatment and also the current treatment policy. Despite all the efforts, the burden of malaria in Tanzania has been on the increase, and current efforts to invest in malaria vaccine development were a welcome initiative.

Project activities

The project principal investigator, Ms Violet Siachinji (TDRC) and Dr. Martha Lemnge (NIMR)



Initiation of Project at Tanga Centre

presented their planned malaria vaccine project activities. They covered the objectives of the project and detailed the specific project activities. Both investigators ended by thanking AMANET for the capacity strengthening grant and pledged to mobilise motivated teams ready to take on the project.

From AMANET

Professor Charles Mgone talked on the place of the two centres in the bigger malaria vaccine development programme. He gave details of AMANET activities across Africa including centres at which training has been done through workshops, the work of the Afro-immunoassay network with its six centres. He indicated that with this grant, TDRC and NIMR were now born in the AMANET family, and will fully be involved in all activities. With this project, the centres should develop to be able to participate in phase I, II and III malaria vaccine trials.

The Managing Trustee of AMANET, Professor W L Kilama talked on the background and historical perspective of the origin of AMANET as African Malaria Vaccine Testing Network (AMVTN). He provided information for the basis for change into the current set up. He emphasised the importance of the capacity strengthening grants in Africa and the expectations that AMANET has for both centres. He emphasised the need to adhere to the project activities as stated in the proposal and also to stick to the budget lines as approved. He further stressed the need to keep the agreed timelines and that any changes to leading project staff or activities would require AMANET approval.



Dr. Ben Chirwa, Director General at central Board of Health, Zambia

The official launch

The Permanent Secretary of the Copper belt province Mr Gabriel Namulambe was the guest of honour representing the Minister of Health. He began his speech by apologising for the absence of the Minister for Health who would have liked to attend the occasion but could not due to other obligations. The guest of honour pledged support of the government of Zambia to the promotion of research at TDRC before declaring the project officially launched.

At NIMR, Mr Malelemba was the guest of honour representing the Ministry of Health. He began his speech by apologising for the absence of the Minister for Health who would have liked to attend the occasion but could not due to other obligations. In his speech, he encouraged the researchers to take advantage of the grant and excel in their work. He further acknowledged the work of AMANET in Africa before he officially declared the project launched.

Facility Tours

At both centres, the launch was followed by a tour of the facilities by all the guests. The various laboratories visited and equipment available shown. Later, the proposed field sites were also visited. Mpongwe district is about 100 km from TDRC. At Mpongwe, the District hospital was explored with highlights at facilities that have been designated to support the project i.e. laboratories, clinical evaluation and

office space, and lodging facilities for the TDRC staff. For NIMR, the field site at Korogwe is about 1 hour away from the Tanga centre. At Korogwe, a courtesy call was paid to the local district authorities. The District Hospital was toured, and staff working on other NIMR projects was briefly met. The team showed the facilities being targeted for use in the AMANET funded project.

The launch was followed by focussed two day training in GCP for the investigator teams. The objective of the training was to introduce the teams to the basics of GCP before the project starts. Only staffs who will directly be involved in the project were involved. The training had been tailor made to fit the basic GCP requirements as applied to clinical research although the immediate work of site characterisation is not a clinical trial. The following are highlights of the topics covered.

Application of GCP in AMANET projects- Roma Chilengi

The lecture gave a back ground of the International Conference on Harmonisation (ICH) and how GCP has evolved and why it is important in AMANET projects. It emphasised the point that the application of GCP is not optional but a must in biomedical research involving human subjects.

Investigator responsibilities- Christine Manyando/Roma Chilengi

This session focussed on the ICH defined investigator responsibilities. Practical activities from the

TDRC/NIMR project were identified that relate to the standard responsibilities as defined by ICH-GCP.

Sponsor responsibilities-Roma Chilengi

The role of AMANET as a sponsor was presented. All the GCP defined responsibilities explained so that the teams are able to demand for what they understand as sponsor responsibilities even in other projects funded by other sponsors.

Ethical issues in malaria vaccine development- Charles Mgone/Wen Kilama

This talk touched on the fundamental ethical principles governing biomedical research involving human subjects. It then focussed on current issues relating to vaccine development such as the informed consent process, future access to the vaccine, investigator obligations to the communities and participants and matters pertaining to participant specimen.

Overview of GLP in laboratory work- Chares Mgone

This session also took the team through the historical evolution of good laboratory practice to its present application in biomedical research. Specific activities of a GCP compliant laboratory were laid out as the required standard for this project. Highlights included staff safety, equipment calibration and maintenance, quality control, laboratory normal ranges, reagents and specimen storage and archival.



Initiation of Project at TDRC Ndola

Role of Standard Operating Procedures (SOPs)-Charles Mgone

Standard operating procedures were defined as tools that one uses in a standard manner during the course of their routine work. These are stepwise instructions of how a specific task is accomplished and they have become an extremely important tool in GCP. The various applicable standard operating procedures were identified.

Procurement and Accounting Procedures-Badru Amri

The subject of following sponsor regulations and meeting obligations was addressed in this talk. The critical procurement procedures needed for purchases of various thresholds were presented with

emphasis on the requirements of the European Commission as the source of funding. Reporting requirements were also presented emphasising that the technical and financial reports should always be in synchrony.

Data management for product development-Roma Chilengi

The teams were taken through the need for a good data management system. It was made clear that the whole process requires quality control checks and a good quality assurance system must be implemented from the beginning to the end. General principles of data management were presented focussing on the need to generate, collect, analyse, store and report data which is credible.

Presentation of teams and tasks

Following the lecture type presentations, round table discussions were taken to allocate the project team their specific tasks. The specific activities addressing each objective were tackled. The responsible personnel were identified and given the tasks of writing clear SOP's following the lecture from the previous day. The logical framework with "who does what when" was completed.

The projects were to immediately take off following the logical framework, and an agreement for routine monitoring was reached.

Launching of an AMANET-sponsored Vaccination Unit at Balonguen, Burkina Faso

Davy Michel YAGO

On 18 December 2005, the AMANET Managing Trustee Prof. Wen Kilama visited the Centre National de Recherche et de Formation sur le Paludisme (CNRFP) in Ouagadougou, Burkina Faso. The main purpose of the visit was to participate in the launching of a vaccination unit recently built at Balonguen.

Through an AMANET site maintenance grant, CNRFP has constructed a vaccine trials unit at Balonguen village, which is 50 kilometres from Ouagadougou, and is the largest of the 27 villages comprising the DSS sites set up by CNRFP in Saponé district. According to CNRFP, from this humble start upon completion, the unit will comprise of a vaccination centre, a community clinic for providing routine care to patients in the study area and beyond, accommodation for scientists on field work, a water tower, incinerator, a communications centre and an electric power generator.

The opportunity was used to also visit the characterised trial site in Balonguen. This site has already successfully undertaken a phase trial of a malaria candidate vaccine MSP3. The entourage comprised of the invited guest (Prof Kilama) and

CNRFP scientists and was guided by the Principal Investigator for the CNFRP-AMANET Project, Dr Sodiomon Sirima. What was even more apparent during the visit was the participation and acceptance of the project by the local community.



Prof. Kilama (fifth left) and Dr. Sirima (third right) with Balonguen Chief and his cabinet

The next capacity strengthening grant award

During the year, AMANET announced a call for capacity strengthening and site development for malaria vaccine trials. Twelve institutions submitted letters of interest. These were subjected to the pre-set eligibility criteria, through which five applicants were short listed. These include Kintampo Health Research Centre of Ghana; Institute of Endemic Diseases of Sudan, Med Biotech Laboratories of Uganda, Kwame Nkrumah University of Science and Technology of Ghana; and Makerere University of Uganda. These were invited to submit full proposals in a standardised AMANET format. The process of selection is ongoing and the grant award is expected to be announced in January 2006. The selected institution will join the AMANET capacity strengthening programme which already includes three centres from Burkina Faso, Zambia and Tanzania.

Led by their village Chief and his cabinet, the people of Balonguen had come in hundreds to grace the occasion with traditional dances. Prof Kilama was presented with traditional presents including a live sheep and a traditional hat; he also shared in drinking a local brew called "Visitor's Water"

The site tour was followed by introductions and a short overview of the project given by Dr Sirima who also thanked the Chief and Balonguen villagers for their support, acceptance and active participation in the project and for providing land for the construction of the vaccination unit. On behalf of the Balonguen people, the Chief thanked AMANET and the CNRFP team for choosing their village for the project, he urged the funders and project team to continue with this spirit and promised continued support from the village.

Speaking through a translator, Prof Kilama thanked the Chief, his

Cabinet and the people of Balonguen and especially those who have been volunteering in research activities, and for allowing construction of the Vaccine Trial Unit. He called for their continued support and collaboration and urged them to take good care of the health facility being installed in their village which can also be used in future for other studies aimed at bettering the lives of the local community and the nation at large. In concluding his remarks, he promised that AMANET will continue collaborating with CNRFP which in turn will persist in working closely with the people of Balonguen.



Prof. Kilama meets the Chief of Balonguen

Despite the heavy schedule, Prof Kilama seized the opportunity to also meet with the CNRFP researchers, and to pay a courtesy call at the Netherlands Embassy, since the initial AMANET funding of CNRFP was possible through a Netherlands Ministry of Foreign Affairs (DGIS) grant.

Report on the Training Workshop on Data Management for Malaria Vaccine Trials

O. E. Mwerinde, D. Y. Mensah, T. Bandason

A training workshop on Data Management for malaria vaccine trials was organised by the African Malaria Network Trust (AMANET), hosted by the Malaria Research and Training Centre (MRTC), University of Bamako, Mali, starting Monday 26 to Friday 30 September 2005. It was attended by 21 participants (3 females and 18 males) from 13 countries across Africa. The aim of the workshop was to build capacity in data management using Microsoft ACCESS Database Management System in hands-on practical training.

The focus was on malaria vaccine trials as an area of current attention by AMANET.

Introduction

It has been noted that Data Managers play a critical role in clinical trials. However, in the past, their role has been limited to consultation rather than being involved right from the study planning stages. In view of this anomaly, this workshop was designed as a step towards redressing this situation by building capacity of Data Managers to facilitate their full participation and understanding of clinical trials. It was noted that a clinical trial could only be deemed successful if the GCP guidelines have been adhered in the way the data are managed.

Workshop Activities

Day One

Professor Ogobara Doumbo, opened the workshop by welcoming all

participants and then called upon Dr Issaka Sagara (MRTC) to facilitate the introduction of participants and facilitators present.

In his introductory address, Professor Charles Mgone stressed the point that Data Managers must be involved among the decision makers in the team of clinical trials personnel right from the planning stage to the end.

Dr Roma Chilengi, in his session on "the role of Data Management in the clinical trial process", also made some never-to-be-forgotten remarks that should always guide and guard the Clinical Trials Data Manager;

- Errors are inevitable in CTDM but they must be reduced to the barest minimum.
- The Data Manager should be up-to-date with the GCP guidelines
- There is no single activity referred to as Data Management.
- It is a whole process from the collection of the sample to the archiving of the report/data
- Hence the DM should be involved in the whole process to ensure GCP requirements according to ICH-1.46
- Training and re-training is inevitable if GCP is to be maintained.



Workshop group photograph

- The centre's DM process should be ready and welcome audits at any time.

It was observed that there has been a tendency for data managers to work as data clerks, and/or physically fixate on their computers to build databases and not provide input throughout the whole stages of the trial. "Data managers start managing", were the words of Dr Chilengi enforcing the point for the need for data managers to be involved in the whole process of the trial. The lecture on Principles of Data Management by Mr Gerald Feldman emphasized the importance of data managers to involve the whole scientific study personnel of the trial during the process of logical planning and physical designing of the databases. He also added that designing a database should always be preceded with the logical planning on a paper, avoiding the rush to the physical designing activity. In his concluding remarks, Mr Feldman said... "Start small, keep it simple and be flexible".

Dr Allasane Dicko, head of DM at the MRTC, presented a Sample Protocol. This was based on one of the drug trials conducted at the centre and set the scene for later practical work on active reviews of sample CRFs by participants. The participants critically analysed the CRF and discussed findings in terms of questions and field allocations in view of data management requirements. Mr Feldman further laid the foundation for the hands-on practical lessons when he presented



Data management workshop in session

an overview on the use of MS ACCESS in data management. He gave insights into what MS Access offers, giving advantages and disadvantages, and terminologies relevant to the course. Mr Ismaila Thera, then took the participants through practical lessons on designing the data base starting with the creation of data entry screens in using MS ACCESS. The day's activities ended with homework in which each participant was to design and create several screens on his/her database.

Day Two

The second day began with a review on the homework resolving the difficulties that participants faced by themselves. Then the day focused on the tasks of creating tables using the test the provided CRFs. This was a hands-on practical session in which setting relationships and production of a data dictionary were tackled. The participants were all building on their data bases with support from the facilitators.

Mr Feldman gave a presentation on CRF Processing/Entry and Filing. He added that this process involves steps such as receiving CRF, entering data, cleaning data, coding data, reconciliation and transferring data or filing. More homework tasks were given for exercising creation of relationships and coding of data.

Day Three

The next day began with Mr Thera checking the homework from the previous day. Some participants had some problems, which were discussed and resolved. Dr Jan Bart Hak, of Xendo Pharma Design then gave a lecture in which he raised important points on data outliers that brought very interesting discussions. He clarified issues pertaining to databases as they relate to inclusion and exclusion criteria set out in the protocol.

The day's activities continued in two phases interspersed with presentations on "Generating, Tracking, Reviewing, and Resolving Queries" also by Dr Hak discussed the role of the data manager in the process of generating and resolving queries. Pointing correction of mistakes as the intent of raising queries, he emphasised the need for quality control checks in the process of designing the forms, data collection and entry. Major causes of errors were identified and sample data query resolution form discussed. Furthermore, he emphasized that the role of the data manager is not only related to building the database and ensuring that data is entered in it, but that this role is also includes being in contact with the other team members responsible for conducting the trial.

Start Small, Keep it Simple and be Flexible

Dr Mahamadou Thera discussed "GCP and Data Management" where he highlighted the principles of GCP and how they overlap with those of good data management practices. Several references were made for the document of the Society for Clinical Data Management (SCDM) emphasising the minimum standard on data acquisition, privacy, validation and data quality. Best practices were also elaborated as being desirable in the following areas.

Phase I: Hands-on Training Session in the areas of

- Designing the Double Data Entry System
- Designing the Audit Trial System and
- Designing Queries

Phase II: Open Discussion

Dr. Hildur Blythman of the European Malaria Vaccine Initiative (EMVI) coordinated the presentations from participants. Representatives of each centre were called upon to explain issues relating to their centre's infrastructure, software systems, problems encountered, experience in clinical trials and relate future expectations. The following is the summary of the major discussion points from the centres represented:

- The common software that are in use at the participating centres are EpiInfo, MS Access, Visual Foxpro, SPSS, SAS and STATA.
- The data management infrastructure situation varied widely from some which have adequate facilities to others who have no specific room to accommodate data management. Only four of the participating centres reported having their own data servers.
- Most of the participants reported that they are getting involved in clinical trials data management for the first time hence the workshop was very opportune.
- Problems encountered were mostly related to recognition. All participating centres, except two, indicated a less than desirable level of coordination between them and their Principal Investigators (PIs). Typically, their PIs would “do their own thing” and only bring them CRFs and databases (already designed, in some of the cases) to manage.

At the end of the experience-sharing session, there was a brief period of question time and discussions. During this period, Dr Blythman made some important comments regarding the designing of SOPs as regulatory bodies are very keen on these. She urged participants to consider the following points when writing SOPs:

- Decide how to work, and document the procedures of your decision
- Make sure to follow what you stipulated
 - Do not write out what you are not going to do
 - Do not write out what you cannot do

The day's activities were ended with yet again another home assignment.

Day Four

The day began with a presentation of a brief summary of the first three-day's activities by the report-writing team presented by Mr David Mensah. To get participants to appreciate more of the entire process of clinical trials and why the role of the Data Manager is very important, Dr Blythman made a presentation on “Steps taken in Drug Development and the role of the clinical Data Manager”. She

spoke about pre-clinical trials and clinical trials, elaborating what the objectives of each step involved in product development. Mr Feldman gave a talk on protections and data base security providing available options for protecting databases. He began with the physical security, limiting access to facilities and focussed on available firewall barricades that one can install. The need for backing up databases was also discussed. The lecture was followed by an example from the participant from Manhica, Mozambique who shared his specific experience on how he set up a security system at his site.

Mr Thera then presented on “Importing and Exporting Files”. He led the participants through the process of importing and then exporting data into and from the database. Samples were provided for the participants to practice. Dr Hak then spoke about the need of validation of imported and exported data by using some basic statistics, such as the mean and standard deviation, on both the source data and the exported one to ensure that they are the same.

Dr Sagara (MRTC) made a presentation on “The role of the BioStatistician”. He said the Statistician's role also starts from the very beginning to the end and that sampling and data analysis are his/her main roles. He must be involved in articulating the hypothesis and sampling strategies.

Further, the analysis plan must be worked out before the study starts and should be included in the p r o t o c o l indicating all planned interim analyses. On the issue of error checking and specification, he emphasised that Biostatistician s h o u l d collaborate with the Data Manager to generate queries. The talk was followed by discussions related to blinded

randomised controlled trials and activities related to database lock/freeze and query resolution.

The last lecture was also given by dr Sagara on "Quality Control and Assurance in Clinical Trials". His talk included the following:

- In the process of randomisation, the investigator must be particular about selection bias, the major reason why the Biostatistician is very much needed on the team.
- Blinding is also a part of QA and it is important especially where end-points are subjective. Adequate measures must be taken to ensure true blinding.
- Development of CRF should ensure unambiguous formulation of questions.

There was then a brief tour of the MRTC DM facilities. Participants were taken through the various stages of CRF handling as it arrives from the field, the log in procedures shown, data entry, quality checks, and independent audit checks and data storage. Participants visited the data entry room, the data managers' offices and the archival room where the storage cabinets are housed for archiving.

Day Five

Day five began with checking and completing of the participants homework.

The same test questions undertaken on the first day were given as post workshop test. A simple analysis of the results for the distribution of the scores and a paired T-Test indicated that there was a significant gain from the workshop.

Professor Doumbo, Professor Mgone and Dr Thera each gave closing



Mensah-Yao asking a question

remarks. Mr David Yao Mensah and Ms Akaragwe Ateh Isabel thanked the organisers, for a well organised and thoroughly enjoyable workshop. They emphasised that these are

worthwhile events, and participants hoped to be able to attend other workshops in the near future where their PIs and other players in the study would be involved to

openly address the marginalisation issue.

The closing ceremony included the handing out of certificates with all the facilitators and organisers present.

Distribution of marks (out of 20)

Score	Pre-test	Post-test
Mean	12	15
Max	15	18
Min	8	11

Paired T-Test for gain in mean score

Mean gain Post-Pre	T- value	p
3	8.35	<0,0001



Hands on assistance among practical session

Report on the Training Workshop on Protection of Human Research Participants: Writing of Standard Operating Procedures (SOPs) for Ethics Review Committees in Eastern Africa

Titus Kabalimu, Charles Wanga, Bertha Maegga, Joseph Mthetwa

AMANET in collaboration with the Office for Human Research Protections (OHRP) of the US Department of Health and Human Services organised a three-day training workshop on "Protection of Human Research Participants: Writing of Standard Operating Procedures for Ethics Review Committees in Eastern Africa". The workshop which was held on 29-31 August 2005 in Dar es salaam, Tanzania attracted a total of 13 participants from ethics review committees (ERCs) and institutional review boards (IRBs) in Ethiopia, Kenya, Sudan, Tanzania, Zambia and Zimbabwe. The course facilitators came from AMANET, OHRP, and the Tanzania Commission for Science and Technology.

The main objective of the workshop was to contribute to the development of high ethical review standards for African institutional and national ethical review committees through the development of reference standard operating Procedures (SOPs) for ERC's and IRBs. This was a demand-driven hands-on workshop where participants were guided to develop as well as improve SOP's for

their ERCs/IRBs. The workshop was divided into four sessions namely: Principles of ethics review and role of ethics review committees; Standard operating procedures; Designing standard operating procedures; Accreditation and monitoring of ethical review practises in Africa.

Principles of ethics review and the role of ethics review committees

This session comprised of presentations on fundamental principles of health research ethics: respect for persons, beneficence and justice; regulations governing human research participation and group work.

The session being on the first day, was preceded by an opening speech by Prof Wen Kilama, AMANET Managing Trustee.

This was immediately followed by a



Lecture on Principles of Ethics Review and the Role of Ethics Review Committees in progress

talk on Fundamental principles of health research ethics: respect for persons, beneficence and justice. In this presentation, the history and developments on issues pertaining to health research ethics from the times of Hippocrates were presented. They included the Nazi Germany experiments, the Nuremberg Trials and the Nuremberg Code of Medical Ethics and the post-war response and agreements which culminated into the 1964 Helsinki Declaration. Despite establishment of such regulations, major flaws continued to

happen in the practice of ethics in research involving human subject; the Tuskegee Syphilis Study in the US was cited as one recent example, other similarly recent examples of abuse of ethical practice cited include several clinical trials Africa, such as the Trovan clinical trial in Nigeria and the Mefloquine clinical trial in Gabon, Zambia, Uganda and Kenya.

The three basic principles in biomedical research (respect for persons, beneficence and justice) formed the core of the presentation. Emphasis was placed on the need to protect vulnerable persons (e.g. pregnant women and children, the disabled, the rural poor). Informed consent and its elements (disclosure of information, understanding, voluntary authorization and competence) were also highlighted.

In the second presentation, US Department of Health and Human Services (DHHS) regulations for human participation in research were presented by Dr Edward Bartlett. It was mentioned that regulations governing human participation in research besides ensuring subject protection, they aim to educate researchers about human subject protection, and are harmonised to assure consistency in the manner in which human subject protection can be achieved across different studies, while guiding ethics committees reviewing research protocols. Regulations also provide a framework for developing institutional SOPs.

It was mentioned that all human research work funded by DHHS is required to comply with the "Common Rule" which was said to be a US Federal Policy for the protection of human research subjects. It was further emphasized that before setting out to review a submitted proposal, ethics review committees need to verify whether the proposal is actually research. Once this is established, the next question should be whether research involves human subjects and should be at a minimum risk. In the DHHS common rule, research is defined as "a systematic investigation designed to develop or contribute to generalisable knowledge". Systematic means a plan and a data collection form to collect information in a uniform way; contribution to

generalisable knowledge implies an intention to present the findings at a professional conference or scientific publication.

The presentation also described obligations and responsibilities of research institutions and IRB. When reviewing research protocols, IRBs are required to follow agreed written procedures and the review should be done at convened meetings in which the majority of the members are present. The protocol under review requires the approval of a majority of those members. Other issues covered included informed consent and classification of types of exempt research.

Another presentation in this session was on "The Ethics Review Process" by Prof Charles Mgone touching on such areas as meeting requirements, elements of review, expedited review, communication, follow up and oversight. It was said that the principle purpose of ERC's/IRB's is to safeguard the dignity, safety, rights and well being of research participants (potential and actual). The attributes of ethics committees were mentioned to be independence (freedom from political, professional, institutional or market influences), competence and proficiency.

ERCs should be established in accordance with the applicable laws and regulations of that particular country and should respect values and principles of the community they serve. Membership to ECs should be both multidisciplinary and multi-sectoral, including relevant scientific expertise, a balance in age and gender representation, and also the inclusion of laypersons especially from vulnerable groups. It was further mentioned that ethics committees should establish and follow publicly available SOPs that describe the committee's establishment, terms of reference, functions and internal and administrative procedures. In addition, there must be an established procedure for following-up progress of the approved applications from the time of approval to termination of the research. All documentation and communication of the ethics committees should be dated, filed and



Group work in Progress

archived according to an authorised SOP. This should also apply for document / record access and retrieval procedures.

The presentation was followed by group work where participants were divided into three groups that were assigned to discuss three different case studies, which they later presented in a discussion panel. The group presentations stimulated very involving and lively debates, demonstrating many dilemmas faced in real life situations. The participants found the practical sessions very enlightening and valuable for their committee work.

Standard operating procedures

This session started with a presentation by Dr Rose Kingamkono on "Guidelines on developing and using standard operating procedures (SOPs): writing, updating and archiving". SOPs for Tanzania National Health Research Ethics Review Committee (NHRERC) were presented and discussed. NHRERC has 26 SOPs which outline the processes for authorising, reviewing, archiving and amending study proposals. They also describe the mission, role and functions of the ethics review committee. Some of the SOPs presented include: Confidentiality/conflict of interest; Administration of the committee; Protocol review procedures; Voting procedures; Assessment of protocols; Review of protocol amendments; Expedited review; Use of Data Monitoring Boards; Monitoring and Evaluation of reports; Site monitoring visits; Review of final reports and Management of protocol termination and Revision of SOPs.

In addition NHRERC has developed terms of references to ensure that it operates within specified SOPs.



Olivia Zenda and Rosemary Musesengwa, participants from Zimbabwe

Participants were then divided into three groups which dealt with several different aspects of SOPs. The groups engaged in a task to design and formulate SOPs on:

- Expedited Review
- Informed consent for archived materials
- Conflict of interest in IRB

Each group made a presentation of their drafted SOPs which were discussed, modified and the pertinent issues addressed. This practical exercise was also found particularly instrumental in understanding the complexities involved in designing appropriate SOPs in real life situations, especially in this era of globalisation and rapid scientific and technological advancements.

Accreditation and monitoring of ethical review practises in Africa. The aim of this session was to create opportunity for exchange of views on accreditation and monitoring of ethical practises in Africa, to raise awareness of the need for harmonised standards in ethical review in Africa, discuss what accreditation of ERCs may imply and provide platform for discussion on what should be the best way forward.

Accreditation was defined as an official approval given by an organisation stating that something has achieved a required standard. To meet standards, the accreditation has to be acceptable/recognisable as authentic, independent, devoid of conflict of interest, transparent and ideally it should also be participatory. The rationale, mechanism and terms of reference for accreditations were presented and adequately discussed.

Another important feature in this session was the country reports from participants on their national ERCs or IRBs state of affairs. It was generally noted that although review committees and boards exist in all represented countries, not all their SOPs were well prepared to deal with many issues pertaining to ethics of research involving human participants.

In Tanzania, the NHRERC operates through the National Institute for Medical Research (NIMR) (Tanzania NIMR Act of Parliament No.23 of 1979). NHRERC receives applications for ethics clearance from within and outside the country. The national committee grants ethical approvals (Ethics Clearance Certificate) to principal investigators co-signed by NIMR and the Ministry of Health. NHRERC conducts passive monitoring/oversight by demanding progress reports, and active oversight is now being instituted.

Local/institutional review boards operate through their institutions. They also receive applications from within as well as from national and international collaborators. IRBs are obliged by law to notify NHRERC on approved local health research. Research involving external collaborators has to be forwarded to NIMR-NHRERC for approval. Currently there are nine (9) public and four (4) private institutional review boards.

In Ethiopia, the Ethiopia Science and Technology Commission (ESTC) guides, coordinates, and facilitates all science and technology activities (health research included). ESTC issued a Health Science and Technology policy in 1994, which was followed by the then National Health and Science and Technology Council (HSTC) in 1997. HSTC has various standing committees and the National Health Research Ethics Review Committee (NERC) is one among them. The Health Department of the ESTC in collaboration with the HSTC-NERC has revised the 1997 ethics guideline procedures in 2003.

All health research involving human

participants must be subjected to an independent ethics review by health research ethics review committees. The Ethiopian NRERC is established at three levels; national ethics review committee (NERC), regional ethics review committee (RERC) and institutional ethics review committee (IERC).

In Zimbabwe, health/medical research falls under the jurisdiction of the Medical Research Council of Zimbabwe (MRCZ) and all proposals have to be reviewed and approved by it. Studies that involve the testing of drugs and devices have to be approved by the Medicines Control Authority of Zimbabwe (MCAZ) which is responsible for the licensing of drugs and medical devices. Clinical trials are reviewed simultaneously by the MRCZ and MCAZ.

MRCZ was established in 1974 through the Research Act of 1959 and Govt. Notice No. 225 of 1974 to promote and coordinate medical research. MRCZ is a semi-autonomous specialized council of Research Council of Zimbabwe (RCZ). It reports to Parliament through the Minister of Health & Child Welfare and receives funding from the Government plus one percent levy on approved project budgets as well as donations from well wishers.

The Medicines Control Authority of Zimbabwe (MCAZ) was established in 1969 as the Drugs Control Council (DCC) through the Medicines and Allied Substances Control Act (amended 1997). MCAZ is responsible for the regulation and licensing of medicines and devices, it is comprised of 12 members representing Zimbabwe Medical Association (ZIMA), the Law Society, the Pharmaceutical Society, the Veterinary Association and others. Members of MCAZ are appointed by the Ministry of Health to play role on behalf of the government. It only deals with clinical trials that involve the testing of drugs and devices (Phase I, II & III).

The Ethical Review Committee for the Tropical Diseases Research Centre, in Ndola, Zambia only allows research work that involves human

participants to be conducted under strict compliance with the standard of Good Clinical Practice (GCP), the declaration of Helsinki, CIOMS and other International Ethical Guidelines for Biomedical Research. The committee reviews project protocols/proposals submitted to it through the TDRC Scientific and Technical Committee (STC) for scientific merit and later submitted to the Ethical Review committee for ethical review. Once the review is

complete, any comments or questions arising are communicated to the investigator. This IRB is an institutional organ with an autonomous function and was established through an Act of Parliament. The one other IRB in Zambia based at the University of Zambia, which reviews protocols of health research involving human participants, as well. So far, there is no centrally placed national ethics review board /

committee which links the functions of the existing IRBs.

After country presentations, the Tanzania NHRERC SOPs were once again tabled and from the knowledge accrued through the training, suggestions were made on ways to improve on the standards for reference SOPs for all. In the end, draft SOPs were promulgated, and participants urged to study them and to focus on the sections particularly relevant to their own IRBs.

Workshop on Molecular Biology and Immunology in Malaria Vaccine Development

Dorothy Anum, Mbang Muleba, Sydney Mwanza, Andre Lin Ouedraogo, Charles Wanga

Introduction

This was a three-day workshop preceding the fourth MIM Pan African Conference held from 9 to 11 November 2005 at Prestige Palace Hotel in Yaoundé, Cameroon. The workshop aimed at forming a forum for African scientists working on malaria to gain update information from experts in the field, as well as exchange views and experiences among themselves as part of strengthening of south-south collaboration, mentorship and networking among African molecular biologists and immunologists. By holding the workshop in Cameroon, AMANET provided an opportunity for young African scientists to participate in the MIM Pan African Conference.

Overview of malaria immunity

The overview of malaria immunity set the pace for the subsequent lectures. The presentation touched on essential steps in anti-microbial defence, pathogen recognition, the Toll-like receptors (TLR) family, innate & acquired immunity (in the context of malaria), components of innate immunity, bridging innate and acquired immunity, Memory T cells and identifying central memory T cells (TCM associated with malaria vaccine-induced protection, Factors affecting the outcome of Pf infection in African children and Pregnant Women and the Principles of Malaria vaccines. The lecture also touched on the issue that children with sickle cell (HbAS gene) had significantly higher levels of antibody with specificity for neo-antigens.

T-cell immunity

In this presentation, malaria immunity was said to be an essential step in malaria defence. In malaria, as in other diseases, cell mediated immunity appears to be crucial for prevention and control. T-cell immunity depends on both CD4+ and CD8+ cells recognizing presentation of exogenous and endogenous antigen

epitopes. Cell mediated immunity (T-cell immunity) in malaria targets infected hepatocytes and asexual blood parasite multiplication. It was also established that the effector T-cell responses are driven by IFN-gamma release and that T-cells play a pivotal role in elimination of exoerythrocytic or liver parasite stages through the activity of CD8+ and CD4+ cells. The presentation gave results of a study in Gabonese children which showed that LSA-1 induced IFN-gamma responses reflecting immunity to malaria.

B-cell Immunity

B-cell immunity exists although it offers partial protection. The magnitude and nature of immunity depends on parasite and host genetic factors with the parasite manipulating the response. Antibodies released by B-Cells were said to be important acting in a stage-specific fashion (sporozoites, merozoites, red blood cell forms, gametocytes). Malaria pathogenesis was said to be largely an immunological response triggered by the release of schizont exoantigens and TNF inflammatory inducers linking TNF to the clinical presentations of the disease.

Malaria immunity in pregnancy and cellular immunological responses of new-borns

In this presentation malaria was said to be one of the main causes of high maternal mortality & morbidity as a result of severe anaemia in unknown numbers of pregnant women in endemic areas. The plight of malaria on the



Group photograph

infancy was also pointed out and in this case malaria is associated with low birth weight and up to 200,000 deaths per annum. Malaria in pregnancy was said to be a result of molecular adhesive interactions between parasite ligands on infected erythrocytes and host receptors expressed on placental syncytiotrophoblasts. The interactions are mediated by molecules on syncytiotrophoblasts, including chondroitin sulphate A (CSA) and hyaluronic acid (HA). Primigravid mothers were said to have a greater risk of placental *P. falciparum* infection because they lack antibodies that interfere with binding of parasitized erythrocytes to syncytiotrophoblast receptors (CSA/HA). The impact of pregnancy associated malaria and the additional public health burden was also discussed.

Role of AMANET in malaria vaccines development in Africa

The role of AMANET in malaria vaccines development was the final talk for the day, highlighting the burden of malaria in Africa and pointing out methods used for malaria intervention which have so far been inadequate to contain the scourge, and therefore calling for new strategies such as vaccines.

Vaccine development is a costly and time-consuming process which can take up to 20 years or more before the product becomes available. African participation in vaccine development process has been low because of malaria R&D weakness in most of African health research institutions. AMANET's role is that of building capacities of African R&D institutions and preparing them to conduct malaria vaccine trials, while at the same time promoting south-south cooperation. AMANET also supports the Afroimmuno Assay (AIA) network whose role is to develop validated and standardized assays for evaluating candidate malaria vaccines.

Malaria Vaccines

Day two kicked off with an overview on the history of vaccines and the advances achieved in this regard. Immunology was said to have started around 1000AD. Records from the Orient show evidence of variolation practises where small contents of smallpox pustules were inoculated intra-nasal for purposes of inducing immunity. In 1796 Jenner demonstrated that, because of host specificity of virulence, an animal virus can (sometimes) provide an aborted infection in humans leading to reasonable protection against a human virus. Louis Pasteur introduced the term vaccine in honour of Jenner and his work. These efforts culminated into smallpox being the first and only communicable disease to be completely eradicated by vaccination by the end of 1977.

Development pipeline of candidate malaria vaccines: pre-clinical to cGMP production

This presentation discussed the research and development aspect for malaria vaccine from early stages of antigen isolation and definition, antigen validation, development of models and predictive markers, the limited GMP production of the candidate vaccine for clinical trial, the clinical phase Ia, b (safety) & IIa, b (efficacy), Phase III safety & efficacy trials in target population, to the late stages of scaling up the vaccine production, supply, access and utilisation. The role of the European Malaria Vaccine Initiative (EMVI) was also mentioned and includes providing a mechanism for accelerated development

and clinical trials of malaria vaccines in Europe and developing countries and promoting affordability and accessibility of malaria vaccines in developing countries. It was further mentioned that malaria vaccine development needs a clear definition of roles and responsibilities for the sponsor, investigator, inventor; insurance and indemnification, personal and institutional liability. Legal and institutional requirements for the sponsor were said to be governed by legislation in the sponsor's country.

Blood-stage malaria vaccines

In a presentation on blood-stage malaria vaccines, it was mentioned that protective antibodies against variant surface antigens disrupt cytoadhesion between infected erythrocytes and human receptors on endothelial cells. The protective antibodies may act directly on parasite growth by neutralizing receptors / ligands expressed on the surface of the free merozoites or merozoites agglutination. An ideal vaccine against blood stages should contain epitopes that are recognized by human antibodies which act through biological mechanisms that are effective only in clinically immune individual. Evidence was presented from studies which have identified targets of merozoites neutralizing antibodies; the targets include the merozoites surface antigen-1 (MSP1) and whose protection was said to depend on the relative amount of cytophilic subclasses rather than on the total quantity of immunoglobulins.

Pregnant associated malaria

This presentation discussed the consequences of pregnancy associated malaria to both the mother and the foetus. It was further said that primigravid women are more susceptible to malaria compared to secundigravid or multigravid women and that pregnancy associated malaria (PAM) is sex specific. Sera from secundigravid and multigravid women significantly inhibit binding of parasites to clonal specific antigens (CSA) in vitro. On CSA, the presentation concluded that CSA-selected parasites are not recognised by males; they very well recognised by 3rd-trimester pregnant women from a malaria-endemic area; levels of PfEMP1CSA-specific antibodies depend on parity and levels of

PfEMP1CSA -specific antibodies are positively associated with birth weight and maternal haemoglobin levels.

Regulatory Issues in Malaria Vaccine Research & Development

The last day began with a presentation on Regulatory Issues in Malaria Vaccine Research & Development. Regulatory Authorities (RA) are empowered by governments or international organisations, to decide on and promulgate laws to evaluate product data on its quality, safety and efficacy. The talk pointed out the weakness in most of RA in sub-Saharan Africa and the efforts being undertaken to strengthen them. Since product development is undertaken with a view to eventually register and market a product, product developers need to be informed of regulatory requirements. Early consultations with the corresponding RA is a pre-requisite for proper conduct of the development process.

Immunological correlates in the evaluation of malaria vaccines

Clinical phase II trials offer the opportunity to assess the predictive value of the various in vitro assays, validating immunology and immunogenicity of the T-cell controlled antibody productivity. It has been argued that antimalarial immunity against blood stages is age dependent. Passive transfer of IgG was related to clinical protection by reducing parasite multiplication and hence morbidity. Moreover, IgG3 was said to be short-lived and could explain why antimalarial immunity is not long lasting.

Role of the Afro-immunoassay initiative in evaluation of malaria vaccines in Africa

The Afro-Immuno Assay (AIA) aims to develop standardized assays using the same reagents and statistical tools to assess the relationship between acquisition of malaria specific antibody responses to potential malaria vaccine candidate antigens and protection from clinical malaria. Standardized assays developed by AIA can be used to validate malaria candidate antigens, provide essential baseline information for clinical trials and enhance quality assured laboratory capacity and capability.

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