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PRESS RELEASE



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**FIRST CLINICAL TRIAL OF THE MALARIA MSP3
VACCINE IN AN ENDEMIC AREA CONDUCTED
BY THE CENTRE NATIONAL DE RECHERCHE
ET DE FORMATION SUR LE PALUDISME
(CNRFP), BURKINA FASO**

Since October 2003, the *Centre National de Recherche et de Formation sur le Paludisme* (CNRFP), Ministry of Health, Ouagadougou, Burkina Faso is conducting the first clinical trial of MSP3 malaria vaccine candidate in a malaria endemic area. This phase 1b trial is aimed to assess the reactogenicity and the safety of MSP3, in healthy male adults naturally exposed to *Plasmodium falciparum*. The trial is entirely run by a Burkinabè research team from CNRFP. This trial is the result of a fruitful partnership between CNRFP, the African Malaria Network Trust (AMANET) and the European Malaria Vaccine Initiative (EMVI). AMANET is the funding agency and EMVI is the sponsor of the trial.

The candidate MSP3 vaccine has been discovered by the *Institut Pasteur*, Paris, France. This vaccine has already been assessed in a phase 1a clinical trial in healthy adult Swiss naïve volunteers. This trial showed that MSP3 vaccine candidate is safe and immunogenic. Based on those promising results, it has been decided to pursue the clinical development by carrying out a similar trial in a malaria endemic area, hence the current trial in Balonguen, Burkina Faso.

The trial involves 30 healthy male volunteers aged 18 to 40 years. Trial participants are randomly distributed in 2 groups of 15 each. One group received the malaria vaccine (MSP3) and the second group (control) received tetanus toxoid vaccine.

Each volunteer will receive a total of 3 doses of the vaccine administered according to the following schedule: month 0, 1 and 4. Trial participants will be followed-up over one year to assess the safety and the immune response to MSP3. To date, each participant has already received 2 doses of vaccine and everything is going very well.

The Minister for Health of Burkina Faso, His Excellency Mr. Alain Bédouma Yoda stressed out the need to encourage the research on malaria vaccine in Burkina Faso, where malaria remains a major public health problem, being responsible every year, for at least 20,000 deaths in children under five years. Therefore, this current malaria vaccine trial should be strongly encouraged and supported.

The CNRFP is specialised in malaria research and one of its missions is to provide technical support for the implementation of the National Malaria Control Programme through research and training. The CNRFP is part of several international networks in malaria research, including AMANET.

As stated earlier, the MSP3 vaccine trial in Burkina Faso is entirely funded by AMANET, a network of African and allied research institutions working in the field of malaria research. AMANET strives to strengthen research capacity in African research institutions in order to enable them to conduct clinical trials in compliance with international ethical and regulatory requirements. The main mission of AMANET is to promote the evaluation of new malaria control tools in Africa. The current vaccine trial is sponsored by EMVI, a European initiative receiving European public funds to promote the development of effective and affordable malaria vaccines for malaria endemic countries.

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Introduction

The School of Public Health and Social Sciences (SPHSS) is one of the five schools of the Muhimbili University College of Health Sciences (MUCHS), others being schools of Medicine, Dentistry, Pharmacy and Nursing. The school was established in July 2003 after the amalgamation of the former Institute of Public Health, the Institute of Developmental Studies and that of Primary Health Care and Continuing Education. The Institute of Public Health, however, dates back to July 1991 when the then faculty of medicine of the University of Dar es Salaam was upgraded into a college. Currently the SPHSS has five departments namely, Behavioural Sciences, Community Health, Developmental Studies, Epidemiology and Biostatistics, and Parasitology and Medical Entomology.

Within the current School mandate, it is envisaged that some of the departments will expand and develop into two or more independent units or departments. The SPHSS prides in the versatility of its academic staff, but needs strengthening in areas of molecular biology, immunoparasitology and malaria molecular genetics. Currently, the School has 31 academic members of staff with postgraduate qualifications in biostatistics, demography, epidemiology, entomology, health economics, medicine, parasitology, sociology and public health engineering. The strength inherent in the prevailing varied disciplines of the institution linked by a common mission, creates a unique multidisciplinary environment within the University College. In addition, the SPHSS benefits in its academic and research undertakings from interacting with sister schools and institutes.

The Mission of the SPHSS

The mission of the SPHSS evolves from the mission of Muhimbili University College of Health Sciences, which is primarily to provide and sustain in Tanzania a place of learning, education and research in health sciences, and through these to provide a service of a quality required and expected of a university institution of the highest standard. Specifically the mission of SPHSS is inherent in the challenges of the health system of Tanzania.

The challenge to the health system in the country is to promote, improve and maintain the health of Tanzanians to a maximum level possible through organized actions of the society.

The SPHSS aims to address this challenge by developing an integrated spectrum of activities focused on education for public

health professionals, research for evidence-based decision making, management of health systems, technical services related to these education and research functions and advocacy through information, education and communication, thereby increasing the capacities of communities to maintain their own health.

Teaching and research activities

The SPHSS is the College's major resource for undergraduate and postgraduate teaching and research in public health. It contributes to the training programmes in the Schools of Medicine, Dentistry, Pharmacy, Nursing and the Institute of Allied Health Sciences. In addition to participating in the college-wide teaching of undergraduates and postgraduates, the SPHSS offers a Bachelor of Science in Environmental Health Sciences degree and Masters of Public Health (MPH). There are also plans to develop and initiate Masters of Science and Doctor of Philosophy degree programmes. The School also runs short courses of one to three-weeks duration in Research Methodology, Financing and Financial Management of District Health System and on Laboratory Diagnosis of Parasitic Infections. The SPHSS equips public health candidates with skills to provide leadership to district and regional health management teams and in the shaping and implementing health sector reforms. The SPHSS offers an excellent environment for national and international collaboration where community, laboratory and social sciences are integrated to address broad issues of public health.

Major research programmes in the School are multidisciplinary and collaborative, ranging from basic laboratory studies to applied public health research. The focus and orientation of the research has of necessity been on the diseases of major public health significance in Tanzania in particular and the sub-Saharan Africa in general. The major research programmes are focused on several aspects of HIV/AIDS, malaria, reproductive health, intestinal helminthiasis, school health, transmission dynamics of plague, lymphatic filariasis and demographic surveillance.

Currently, SPHSS has long- and short-term collaborative research projects with other institutions including the University of Umea and the Karolinska Institute in Sweden, the University of Bergen in Norway, the University of Texas and Harvard University in the USA and the University of Heidelberg in Germany. On the local scene the SPHSS collaborates with the Sokoine University of Agriculture, the National Institute for Medical Research, the Ministry of Health and the Social Science and Medicine unit of the University of Dar es Salaam.

Malaria Research

Malaria is holoendemic in most parts of Tanzania with over 90% of the population at risk. It is still a leading cause of hospital attendances and deaths and in some localities it causes mortality rates of over 30% in under-fives. *Plasmodium falciparum* is responsible for over 90% of the malaria infections. The major vectors are *Anopheles gambiae ss*, *An. arabiensis*, *An. funestus* and *An. merus*. Transmission is intense and entomological inoculation rates (EIR) of over 300 per person per year have been recorded in some localities.

The approach to control has mainly been early diagnosis and prompt appropriate treatment. This strategy has, however, been frustrated by the emergence of drug resistance in Tanzania.

Resistance to chloroquine (CQ) in the country was confirmed in the early 1980s. By the end of 1990s Sulfadoxine/Pyrimethamine (SP) was recommended as the first line drug for malaria treatment replacing CQ, since the treatment failure with the latter had reached levels above 50% in some places. Resistance to SP has, however, already been reported in some parts of Tanzania and this is a further challenge to the scientific community to search for alternatives.

Malaria research in the SPHSS in the last two decades has therefore naturally focused on issues related to the detection and monitoring of anti-malarial drug resistance, clinical trials on alternative antimalarials and improvement of malaria case management at various levels of health care. Scientists in the SPHSS are currently participating in a major project on quality of malaria case management in under-fives in Primary health care (PHC) institutions in Bagamoyo and Kibaha Districts. This is a collaborative project of MUCHS and the Karolinska Institute in Stockholm, Sweden.

In the search for alternative control approaches, the then Institute of Public Health had conducted some of the formative research on efficacy, impact and operational issues related to the use of insecticide treated nets (ITNs) as a vector control measure in the coastal area of Bagamoyo. This project that was funded by USAID was conducted in collaboration with the Johns Hopkins University of USA.

Other entomological studies have included the characterization of the malaria vectors in Bagamoyo with respect to their ecology, behaviour, transmission dynamics and susceptibility to insecticides.

The School is excited by the unfolding research collaboration with the Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso and the Noguchi Memorial Institute of Medical Research in Ghana and other institutions involved in AMANET-supported research programmes. It is envisaged that within the AMANET programmes the scientific and technical staff at SPHSS will undergo short- and long-term training for capacity strengthening. The contribution of AMANET in capacity building and institutional strengthening has already been realized through short-term training of the scientists in MUCHS and SPHSS in areas of Good Clinical Practice, Molecular Biology and Immunology, and Good Clinical Practice for African Clinical Monitors and Health Research Ethics.

SPHSS is a beneficiary of an AMANET grant for capacity strengthening in site characterisation and testing of malaria candidate vaccines at its Bagamoyo Teaching Unit. The grant is for determining baseline data on sociodemographic characteristics and malaria epidemiology relevant to vaccine trials at the Bagamoyo field-site, as well as for the renovation of the field laboratory and the rehabilitation of the unit so as to accommodate personnel for vaccine trials.

It is envisaged that, the proposed studies and collaboration in developing sites for testing malaria candidate vaccines will also enhance internal research collaboration between the SPHSS and other sister schools of Muhimbili University College of Health Sciences.

**TRAINING WORKSHOP ON HEALTH
RESEARCH ETHICS IN AFRICA
15-19 September 2003, Biotechnology Centre,
Yaoundé 1 University, Cameroon
N. M. Tsotsi, E. N. Shu, R. Musesengwa, S. Farley,
C. O. Agomo, P. S. Igbigbi, M. Limo**

Introduction

The sixth training workshop on health research ethics in Africa was held in Cameroon from 15 to 19 September 2003. The purpose of the workshop was to strengthen further the human capacity base on health research ethics in Africa. At the workshop 13 African countries were represented. These included Burkina Faso, Cameroon, Ethiopia, Gambia, Ghana, Kenya, Malawi, Mali, Nigeria, South Africa, Tanzania, Uganda and Zimbabwe. Additionally there was one participant from the United States of America.



Rationale

The workshop provided an educational framework for understanding and appreciating principles and guidelines of ethics that govern health research and intervention trials in the world today and apply them to the African context.

Objectives

The primary objective of the workshop was to provide a general overview of ethics of health research in the international sphere as well as in Africa. This was realised through review and discussions of various themes including:

- History of health research ethics
- Ethics codes and guidelines
- Responsibilities, composition, functions and operations of Ethics Review Committees (ERCs)
- Ethics principles guiding health research and their application within African settings
- Qualifications, roles and functions of the sponsor, principal investigator and monitor
- Ethical considerations in the design of health research projects
- Analysis of risk/benefit in health research
- What is owed to research participants and communities

- Role and conduct of informed consent process
- Standard of care and fair distribution of benefits and burdens
- Current ethics review mechanisms in Africa
- Availability of products following research and patenting
- Role of regulatory agencies in health research

Facilitators

Banson Barugahare, Makerere University, Uganda, Francis Crawley, European Forum for Good Clinical Practice (EFGCP), Belgium, Wen L. Kilama, African Malaria Network Trust (AMANET), Tanzania, Charles S. Mgone, AMANET, Tanzania, Paul Ndebele, Medical Research Council of Zimbabwe (MRCZ), Zimbabwe, Godfrey Tangwa, Yaoundé 1 University, Cameroon.

Programme

The five-day programme comprised lectures followed by several interactive breakaway group and joint plenary discussions.

Day 1: Introduction to principles of health research ethics in Africa, from the historical background to bioethics in the African context

Day 2: Examining the origin of health research ethics and the standard of care in the African context

Day 3: Ethics in the design of health research, individual autonomy, role of the community and informed consent

Day 4: Good ethical review practice and the role and structure of Ethics Review Committees in Africa

Day 5: Ethics and the framework for health research in Africa - the appropriate framework for carrying out research in Africa and the way forward after the workshop

Workshop proceedings

Day 1

The participants were introduced to some of the fundamental principles in health research ethics. Presentations dealt with concepts of African and western health research culture and how these systems differ. Participants were sensitised to cultural differences surrounding bioethics, and what can arise when those differences are not respected and understood. In the discussion that followed, participants agreed that ethics should not compromise scientific integrity, but form the backbone of science. However, this may impose certain standards on good scientific inquiry. Ultimately, what is owed to health research participants is respect, honest and detailed information about the research and benefits from the research process.

Day 2

The day started with a group discussion in which participants sought to find a balance between science and ethics when designing clinical trials, bearing in mind the concepts of randomisation, blinding, placebo, equipoise, trials in children and pregnant women. The discussion was amplified in the presentation on the standards of care and how this should be applied in Africa. Recognizing international, regional and local disparities in the existing care, participants grappled with the question of how to apply the international best standard of care within health research constraints in Africa.

Day 3

The day addressed the appropriateness in design of health research. At the heart of this challenge lies the concept of informed consent, which relates to individual autonomy and the role of the community. From the discussion, an important unresolved issue was how to ensure informed consent in the African context given differences in literacy, history, culture and also the inherent unquestioned acceptance of research by participants. The group discussion was centred on deciding research priorities in view of the importance of safeguarding vulnerable communities.

Day 4

The day began with presentations on the structure and establishment of ERCs in Africa. Topics comprised the composition, operation, funding, review, inspection and audit of these committees. During the discussion, concern was raised on the potential conflict of interest among institutions that manage ERCs. Regarding training, participants stressed the need for incorporating ethics in undergraduate curricula as well as availing members of ERCs, additional courses and workshops.

Day 5

Day 5 emphasized on the distinctions between public- and private-funded health researches and addressed methodologies for encouraging ethical public-private partnerships. In discussing public-private partnership the groups discussed the complexities of national health research systems and the need for establishing clear priorities at local, district, regional and national levels. The challenge is how to effectively promote African health research priorities in the international context.

Critical issues brought up during the course of the week

Other central issues brought forward during the week included the strengths and weaknesses of international health research ethics doctrines. In particular, participants noted the ongoing debate between local and universal ethics. Additionally, issues such as ethics in the genomics era, animal experimentation, social science research, intellectual property rights and the 10/90 gap were also given due attention.

Workshop outcomes

Following the workshop, participant made some key decisions and affirmations. These were:

- In places where they do not exist; Ethics Review Committees should be established, and where they are weak; they should be strengthened
- Members of Ethics Review Committees should be well-trained in health research ethics
- Ethics Review Committees must be well-financed, independent and have their actions and decisions audited. They must ensure that approved proposals have a component for strengthening health research capacity in Africa
- It is the primary responsibility of Ethics Review Committees to ensure that research participants are well informed, empowered and protected
- Public-private partnerships must be sought, cultivated and strengthened to respond to Africa's health research needs

- Sponsors have a social responsibility to act ethically
- Researchers must promote health research ethics at all the times
- Profit-seeking can no longer be the ultimate objective of health research in Africa
- Researchers should not seek compensation at the cost of participants' well-being
- Governments have the responsibility of funding and monitoring research according to their national priorities
- Participants affirm the need to enact in their countries all of the aforementioned decisions.

Outstanding questions and concerns

There were also some outstanding issues. These included the following:

- How should individual participants rally the support needed to catalyse the formation of ERCs in their countries?
- How should the question of where to establish the national ERC in a country with many research institutions be resolved?
- How can funding and membership of ERCs be maintained?
- What mechanism should be used to ensure that benefits of research are provided to communities after the conclusion of the research?
- What is the position of developing countries regarding the standard of care, benefits of research and international codes and guidelines such as the Helsinki declaration and CIOMS?
- How should objectives and motivation of health research institutions and individuals at international and local levels be harmonised?
- What role can PABIN and other regional groups play in developing health research ethics more efficiently?

Recommendations – the way forward

At the closure of the workshop participants looked to the future and asserted the importance of AMANET and its role in building human and institutional capacity in health research ethics in Africa. Participants were asked to proselytise for the cause of health research ethics committees in their own countries. Specific recommendations for the way forward were:

- To establish an on-line course for health research ethics training
- To start in-country training modules at specific institutions in order to facilitate the nurturing of health research ethics committees, and
- To solicit government support for AMANET as a foundation for health research ethics resource for the entire African continent.

Participants departed with motivation to inspire advocacy for health research ethics at their home institutions and keen for an AMANET-organized reunion.

Acknowledgements

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University and the Dutch Ministry of Foreign Affairs (DGIS). The AMANET Secretariat is supported by the European Commission (DG-Research) and the Danish International Development Agency (DANIDA).

AMANET WORKSHOP ON GOOD CLINICAL PRACTICE (GCP) FOR AFRICAN CLINICAL MONITORS

*20-25 October 2003, Hotel Independence, Ouagadougou, Burkina Faso
Joas B Rugemalila*

Introduction

The main objective of the workshop was to train African scientists employed by African research institutions to acquire skills for monitoring clinical and field trials according to the good clinical practice (GCP) standards. There were 21 participants from 10 African countries namely Burkina Faso, Ethiopia, Ghana, Kenya, Madagascar, Nigeria, Tanzania, Gambia, Zambia and Zimbabwe. Of the 6 facilitators, 4 were African scientists.

Programme

Honourable Ailan Yoda, the Burkina Faso Minister for Health was the guest of honour. He commended the efforts of the African Malaria Network Trust (AMANET) in the strengthening of research capacity of African institutions in the development of intervention tools against malaria. He acknowledged AMANET grants to the Centre National de Recherche et de Formation Sur le Paludisme (CNRFP). AMANET funding enabled CNRFP to undertake the ongoing Phase 1b trial of the malaria candidate vaccine MSP3 in Burkina Faso. The workshop programme encouraged interactive discussions on selected topics as follows:

Discovery and development of candidate malaria vaccines - *Dr Joas Rugemalila*

The public health importance of *falciparum* malaria justifies the efforts that are made to develop vaccines against the disease. Human protective immunity against malaria involves multiple humoral and cellular responses, which without continued exposure is short-lived. The parasite has a complex life cycle and mutates rapidly forming many strains. Candidate vaccines therefore have to target several parasite strains at different life-cycle stages and sites.

Good clinical practice principles and guidelines - *Dr Alfred Tiono*

GCP prescribes standards for designing, conducting, monitoring, auditing, recording, analysing and reporting intervention trials. Compliance to these standards assures protection of the rights, safety and well being of human research participants, credibility and accuracy of trial data. The International Conference on Harmonization (ICH) GCP guidelines have been adopted by many institutions and are regularly reviewed to accommodate new developments in health research and changing concepts of human rights.

Stakeholders of intervention trials of candidate vaccines - *Dr Joas Rugemalila*

Stakeholders of intervention trials change and increase at every developmental stage of a product and generally include those from

the previous stages. Stakeholders at the discovery level include the investigators, funders and research institutions. During the pre-clinical testing in laboratory animals the additional stakeholders are usually, the contracting manufacturers for current good manufacturing practice (cGMP) production and animal rights activists. Phases 1 to 3 stakeholders include research sponsors, investigators, regulatory boards, independent ethics review committees (IECs), research institutions, data safety monitoring boards (DSMBs), clinical monitors, target populations and research participants.

Responsibilities of investigators – Dr Christine Manyando

Investigators must be knowledgeable on the test product, GCP, protocol, standard operating procedures (SOPs,) sponsor expectations and regulatory requirements. They have to get ethics approval to be submitted to the clinical monitor together with the approved protocol, information for participants, informed consent forms, CVs of the investigators, product importation authorization and laboratory certificates. They should also maintain an investigator's file, product accountability records, screen reference population for recruitment of the study participants and provide medical care.

Responsibilities of the sponsor – Dr Christine Manyando

The sponsor is responsible for trial initiation, management, financing and quality assurance. Some of these responsibilities may be transferred to a contract research organization (CRO). However, the sponsor is always held responsible for the quality and integrity of the trial by designating an appropriately qualified medical advisor and the principal investigator, as well as providing an investigator's brochure and the protocol. Other responsibilities are the provision of necessary compensation to research participants and investigators, and of the tests, comparison medications, notifications and reports to regulatory authorities, and when applicable the coordination of a multicentre trial.

Independent Ethics Committees (IECs) and their responsibilities - Dr Christine Manyando

The Biomedical Research Ethics Guidelines (CIOMS 2002) discusses the composition and responsibilities of IECs. The primary responsibility of IEC is to safeguard the rights, safety and well being of human research participants. The committee reviews the investigator's documents for compliance with state laws, health research ethics and GCP. The trial documents that need to be reviewed are the protocol and its amendments, SOPs, investigators CVs and other contractual documents. The committee also monitors, mostly through progress reports, the approved trial for compliance to the protocol, amendments and other contractual documents.

Qualifications and responsibilities of study monitors – Dr Odile Leroy

Study monitors are appointed by the sponsor to verify protection of the rights and well being of human subjects participating in a trial. The monitor evaluates trial data for accuracy, completeness and consistency between source documents and CRF as well as compliancy to protocol, GCP and regulatory requirements. Monitors should have appropriate training and be knowledgeable on the investigational product, protocol and the informed consent

form. Monitors are required to undertake monitoring site visits before, during and after the completion of the study. They must use SOPs for their work.

Informed consent process – Dr Hanna Nohynek

The presentation was illustrated by a case study from the Philippines that aimed at introducing new vaccines for acute respiratory infections in the expanded programme on immunization. The process eliciting informed consent ensures participants have all the relevant information on the proposed research and opportunity to ask questions. It should also ensure sufficient time to study the possible choices, understand the information and make a voluntary informed choice. The study informed consent documents should be prepared in simple local language and pilot-tested by focus-group discussions and training of research and local health staff.

Principles of health research ethics - Dr Joas Rugemalila

The Nuremberg Code 1949 and Helsinki Declaration 1964 are landmarks in the evolution of health research ethics. The Helsinki Declaration identifies three basic principles namely respect for personal autonomy, beneficence imposing an obligation to maximize benefits and minimize harms and justice requiring treatment of each person according to what is morally right and proper. Justice is basic to equitable distribution of research burdens and benefits. The CIOMS 2002 universal guidelines first published in 1993 accommodates recent scientific developments, changes in human rights concepts and some issues arising from the HIV/AIDS pandemic.

Clinical development of malaria vaccine - Dr Odile Leroy

Clinical development of malaria vaccine is a complex and long process, which could take up to 12 years. It takes into account available immuno-epidemiological data, target parasite strains, desired product characteristics, regulatory requirements, expected performance and ethics rules. Phase 1 is the introduction of a candidate vaccine into human populations to determine safety, optimal dose and route of administration on a limited number of volunteers. Phase 2 is the initial determination of immunogenicity, also in a limited but a larger number of volunteers. Phase 3 trials aim at more complete assessments of safety and efficacy involving adequately controlled studies and therefore a larger number of volunteers.

Clinical trial designs - Dr Hanna Nohynek

Case control designs facilitate study enrolment, calculation of sample size, randomisation, blinded-measurements, generating quality reproducible results and making clear interpretations. Add-on studies randomise participants on established effective treatment for additional treatment with either the new product or placebo. Withdrawal studies randomise participants showing positive response to the new treatment either to continue with same treatment or start on a placebo. Crossover studies use participants as own controls in two or more treatment sequences. Factorial studies do simultaneous evaluation of treatments when withheld, administered singly and in combination. Parallel group studies allow randomisation to one of two or more arms each being allocated different treatment.

Data Safety Monitoring Board (DSMB) - Dr Hannah Nohynek

The DSMB is appointed by sponsor to assess a clinical trial for

data safety, efficacy endpoints and recommend whether to continue, modify or terminate a trial. DSMB should use SOPs and maintain written records of all its meetings. Qualifications for eligibility to DSMB are expertise in clinical trials and safety, data safety, endpoint diagnostics, biostatistics, and epidemiology. DSMBs are not needed for every trial but should be established when required by a regulatory authority or when a trial is perceived to involve increased risk or when early termination is considered due to favourable or unfavourable results.

Management of adverse events - Dr Hannah Nohynek

An adverse event (AE) is an occurrence to a trial participant of an unfavourable and unintended clinical manifestation or laboratory test result. Indications of causality are the strength of association, consistency, specificity, temporality, biological gradient, plausibility and analogy. This is graded as certainly, definitely, probably, possibly or likely, related or unrelated. An AE is classified as expected if it has been reported before or shows consistency in the trial and serious if fatal, life-threatening, disabling or leads to hospitalisation, or prolongation of hospitalisation.

Clinical trial protocol elements – Dr Odile Leroy

The protocol general information must show the trial title, dated amendments, names and institutional addresses of sponsors, monitors and investigators. The background describes the investigational product, results of non-clinical studies, potential risks and benefits, and the study population. The trial purpose and objectives constitute a separate section. The trial design describes endpoints; procedures for minimizing biases; product formulation, dosage and recommended route of administration; discontinuation criteria; procedures for breaking randomisation codes; statistics as recorded directly on CRFs; criteria for inclusion and exclusion; withdrawal and replacement of participants; and the collection of data and obtaining of specimens. The protocol also describes statistical methods, access to source data and documents, quality control and assurance, ethics considerations, publication and communication policy.

Clinical monitoring visits - Dr Christine Manyando

Monitoring site visits are made to ensure that the trial is conducted, recorded and reported in accordance with the protocol, standard operating procedures, GCP and the applicable regulatory requirements. For monitoring visits before, during and at the end of the trial, the monitor has to abide to the SOPs provided by the sponsor. Pre-study visit ensures investigators have enough time, experience and facilities for the study. During study visits they must undertake source data verification (SDV) and at closing out visits, ensure completeness of the investigator's file, site archiving, and that the sponsor gets all the required documents and all ongoing obligations are met.

Standard Operating Procedures – Dr Odile Leroy

SOPs are written instructions to achieve uniformity in performance of a specific function. Although SOPs are not part of the GCP requirements, together with checklists they simplify the organization and documentation of clinical trials to high GCP standards. SOPs may be for the general study organization, pre-, during-, and end-study activities. An SOP should be numbered, bear a title, state its purpose, show related SOPs, and indicate the responsible personnel

and when and how the procedure is to be carried out. It should also show the version-date, list of replaced previous SOPs, names of the authors and approving authority and the accompanying checklists, numbered accordingly. SOPs should be collectively reviewed regularly and the old versions archived.

Data management and clinical report structure – Dr Odile Leroy

The data management plan should ensure accuracy, completeness, validity, confidentiality and integrity. It should show procedures for data collection, coding, entry, screen-design, validity checks, handling of missing information and query resolution. It should also give details of software and hardware that is to be used, trailing or linking, analyses and presentation. The investigator has the obligation of submitting clinical reports to the ethics review committee, sponsor and institutions hosting the trial. The report should show the protocol number, title, names of investigators by sites, reporting period, and describe study objectives, design, populations, treatment, routes of administration, dose regimens, results and conclusions.

Acknowledgements

The African Malaria Network Trust (AMANET)-organised workshop was funded by DG Research and hosted by the Centre National de Recherche et de Formation Sur le Paludisme (CNRFP). AMANET Secretariat is financially supported by the Danish International Development Agency (DANIDA).

THE AFRO-IMMUNOASSAY NETWORK

Daniel Dodoo

Introduction

The Afro-immunoassay (AIA) project is a network of six African and three supporting European institutions, which is sponsored by the African Malaria Network Trust (AMANET). AIA endeavours to develop standardized assays using centrally supplied reagents and uniform statistical tools to assess the relationship between acquisition of malaria-specific antibody responses to four potential malaria vaccine candidate antigens and protection from clinical malaria. Plasma samples are obtained from studies with similar longitudinal cohort designs from six different geographical and epidemiological settings of malaria disease pattern, ranging from low- to holo-endemicity. The project is coordinated from the Noguchi Memorial Institute for Medical Research (NMIMR), Accra, Ghana, and quality control and assurance performed by the Statens Serum Institut (SSI) in Copenhagen, Denmark. The project is initially funded for two years.

Objectives

The overall objective of the project is to develop and introduce standardized immunological assays that will form part of a set of criteria for the validation of promising malaria vaccine candidate antigens and provide essential baseline information for clinical trials that will enhance good quality assured laboratory capacity and capability. The specific objectives of the AIA project are:

- To develop standardized ELISA assays that measures

humoral immune responses

- To correlate the ELISA values with the immune clinical status of the populations studied in Africa, living under various transmission intensities
- To develop and standardize for use in the field an *in vitro* malaria parasite inhibition assay as a possible marker of the acquisition of clinical malaria immunity.

Expected outcome

The expected outcome of the project is to have a set of commonly agreed Standard Operational Procedures (SOPs) for immuno-epidemiological assessment of malaria vaccine candidate molecules to enable comparison of results from different laboratories. The SOPs will include procedures for quality assurance of methods, equipment, personnel, laboratory and a statistical regression analysis model for age-related increased exposure to malaria.

The antigens for standardizing the ELISA assays are in field trials and include AMA1, GLURP, MSP1-19 and MSP3. They will be used in the formulations meant for vaccination in humans.

This multicentre project has for operational reasons been deliberately kept at a relatively initial low number of participating laboratories. However, other laboratories in Africa are encouraged to participate and will be accommodated as soon as the relevant SOPs and assured quality of performance are in place. Similarly, expansion of antigens to be studied besides the currently proposed four is anticipated.

Activities

The project was started in January 2003 following a five-day workshop held on 27-31 January 2003. The workshop brought together 12 scientists from the six participating African countries namely Burkina Faso, Gabon, Ghana, Senegal, Tanzania, Zimbabwe. Also present at the workshop were the Director of the NMIMR, the Provost of the College of Health Sciences of the University of Ghana, the Chairman of the Board of Trustees of AMANET, two AMANET Secretariat officials and five scientists from the supporting European institutions including SSI, Denmark, the Biomedical Primate Research Centre, Netherlands and the Pasteur Institute, Paris. The workshop comprised two days of oral presentations and three of hands-on Enzyme Linked Immunosorbent Assays (ELISA) using standard operating procedures developed for the project. The objectives of the workshop were to assess the availability and quantity of plasma samples intended for the study; to validate the accompanying longitudinal clinical data; to identify possible missing epidemiological information; and to request participants without the appropriate samples to collect such samples using the suggested AIA longitudinal cohort design. Other objectives of the workshop were to conduct laboratory assays under good laboratory practice (GLP) conditions, which will be established as a "Gold Standard" for immuno-epidemiological studies, to agree on the use of standard reagents and statistical methods for compensation of age-related exposure and to evaluate and approve a suggested SOPs for measurement of antibody levels by ELISA.

After the first AIA workshop all six participating laboratories were supplied with the identical test plasma samples and reagents

to run ELISA using the established SOPs. This was part of the capacity building and training to ensure that all participants were familiar with the use of the SOPs before embarking on the testing of site-specific cohort samples.

The second AIA project workshop was recently held at the NMIMR, Accra on 18-21 November 2003. Participants included two individuals from each of the six partner institutions and one potential partner from the National Institute of Medical Research in Amani, Tanzania. The main purpose of the workshop was to get an update on site-specific AIA designed cohort studies and to evaluate and to compare data on the already performed site-specific tests from the six laboratories. Other objectives were to introduce a curve-fitting program for transforming ELISA optic density (OD) values to concentrations; to perform hands-on ELISA; to train workshop participants on how to use the curve-fitting program on the ELISA data; to adopt a statistical model for data analysis; and to establish data management and publication strategies.



At the end of the workshop it was agreed that only four of the six participating countries had the required cohort samples and accompanying morbidity survey data. It was also agreed that by the end December 2003 or the first week of January 2004 supplies should be sent only to these four laboratories that were ready. The laboratories were required to test positive and negative control plasma samples for isotype and IgG subclass responses against the four antigens in order to establish the range of ELISA ODs and antibody unit (AU) responses. This will partly serve as quality control for the ELISA assays to enable the sites to decide whether assays worked as expected and allow decision making on the repeating of assays.

At the workshop each site performed isotype and IgG subclass ELISA for GLURP using a modified SOP that included the use of 3,3', 5,5-Tetramethylbenzidine (TMB) instead of O-nitrophenylenediamine (OPD), TMB being more sensitive, stable and easier to ship to the sites. The adopted modified SOP will be sent to all sites during the shipment of supplies. Hands-on ELISA data generated using the curve-fitting programme were comparable between participants from all sites that independently performed the assays during the workshop.

Data management was discussed and a specific format was

adopted. It was agreed that statistical analysis of site-specific data would be centralised and done by a consultant at the project coordinator's site. However, all the data generated from each site shall belong to the site and individual participants will decide on authorship of their publications. Regarding sources of antigens used in the project, it was unanimously agreed that authorship will be considered for only one individual per antigen source and that will also depend on active contribution in the study, otherwise acknowledgement will suffice. A joint publication for combined data from all sites will also be done.

Financial and progress report from each site will be sent to the coordinator who will in turn report to AMANET.

As a follow-up to the second workshop, testing of site-specific samples using AIA SOPs and protocols will be done and a statistical analysis workshop conducted. Participants will be trained in application of the adopted statistical methodology on the data generated from their respective sites to enable the understanding of issues involved in the use of appropriate statistical tests in data generated from particular study designs, hypothesis testing and biological significance.

Acknowledgements

The workshops were funded by DG Research and hosted by the Noguchi Memorial Institute for Medical Research (NMIMR). The Afro-immunoassay is supported through a grant from the Dutch Ministry of Foreign Affairs (DGIS). AMANET Secretariat is financially supported by the Danish International Development Agency (DANIDA).

PARTICIPANTS REPORT OF THE TRAINING WORKSHOP ON STRENGTHENING OF PRINCIPAL INVESTIGATORS 1-5 December 2003, Harare, Zimbabwe

Theresa Nkuo Akenji, Dinah Gasarasi, Susan Mutambu

Introduction

The workshop was jointly organized by the African Malaria Network Trust (AMANET) and the Biomedical Research and Training Institute (BRTI) in collaboration with Blair Research Institute both of Harare, Zimbabwe.

Justification for the Workshop

Although the responsibilities of investigators are outlined in the International Conference on Harmonization (ICH) Tripartite Guidelines for Good Clinical Practice (GCP), trial sponsors, national regulatory bodies and the general public, particularly research participants and end users of research products still need to be assured that trial investigators are appropriately qualified. It is absolutely necessary to ensure that all investigators and particularly Principal Investigators (PIs) fully understand their roles and responsibilities and have enough supporting personnel and other resources. They must be well prepared before the initiation of any trial. This includes having in place all documentation and being familiar with procedures of obtaining ethics approval, recruitment of the research participants, safety

monitoring, follow-up and dissemination of the research findings.

Objectives

The goal of the workshop was to enable researchers to understand better and carry out their responsibilities as PIs.

Expected Outcome

At the end of the five-day workshop the participants were expected to have acquired knowledge and skills on:

- Properties of malaria candidate vaccines
- Required personnel, documentation, facilities and timescale for conducting trials
- Study design, obtaining of informed consent and recruitment of research participants
- Data management (collection, storage, confidentiality, analysis, archiving and dissemination)
- Adverse event reporting
- Quality assurance and quality control
- Follow-up after completion of a trial

Participants

Twenty seven investigators from various countries including four from Cameroon, two from Côte d'Ivoire, one from Ethiopia, three from the Gambia, four from Ghana, one from Madagascar, two from Mali, five from Tanzania, two from Uganda and three from the host country Zimbabwe were selected to attend the workshop.



Facilitators

Facilitators who were from various African countries included Prof. Wen L. Kilama (AMANET Secretariat, Tanzania), Prof. Anthony Butterworth (BRTI, Zimbabwe), Prof. Charles S. Mgone (AMANET Secretariat, Tanzania), Prof. P. Mason (UZ/BRTI, Zimbabwe), Dr A. Tiono (CNFRP, Burkina Faso), Dr Roma Chilengi (TDRC, Zambia), Prof. Simba Rusakaniko (UZ, Zimbabwe), Mr Honorati Masanja (TEHIP, Tanzania), Prof. Z. Chirenje (UZ, Zimbabwe), Prof. Nathoo (UZ, Zimbabwe), Dr D. Dodoo (NMIMR, Ghana) and Dr William Mwatu, GlaxoSmithKline (Kenya).

Programme

The workshop consisted of presentations from facilitators followed by group and plenary discussions.

Workshop proceedings

Presentations and discussions were focused on the following themes:

1. Role of the Principal Investigators before initiation of a research project

It was emphasized that the responsibility of the PI begins with grant preparations. Once the grant is submitted and approved for funding, the PI is also responsible for the project implementation, budget management (equipment, supplies, and welfare of the staff), publications and writing of scientific and financial reports (progress and final reports). In trial studies the PI prepares and/or ensures the availability of all essential documents (the protocol, memorandum of understanding, contract, confidentiality agreement, investigator's brochure, safety information, consent forms, case report forms, serious adverse event reporting forms and standard operating procedures). Some of these documents are prepared before, or during and also after conducting the trial. Essential documents individually and collectively permit the evaluation of conduct of a study and quality of the data produced.

The group and plenary discussions that followed focused on defining the responsibilities of researchers and sponsors in health research to participants and their communities. It was agreed by all that right from the beginning of the study, the research participants and their community must be aware of the kind of care, treatment and benefits involved. The appropriate standard of care was considered as the best standard of practice in the place where the study is taking place. The research participant should also be fully informed on all aspects of the trial (adverse effects, confidentiality, withdrawal, safety, rights and the outcome of the study).

2. Data management, safety monitoring and reporting

The concepts underlying data management, safety monitoring and reporting were highlighted during the second session. Confidentiality and its role in clinical trials was underscored and defined as prevention of disclosure to other than authorized individuals of a sponsor's proprietary information or of a research participant's profile (ICH/GCP E6). Confidentiality in clinical trials safeguards the respect, justice and privacy of trial participants. The current ICH/GCP demands that data from non-compliant research should be rejected for publication and that the consent information must assure the research participant of confidentiality. The confidentiality declaration by way of signed documentation is also a requirement of ICH/GCP and the signed confidentiality form must have the institutional authority to be able to take disciplinary action in case of breaches.

Data management is a critical component in clinical trials. It should start early during the development of the protocol. The main elements of data management include form designing, data processing plan, data flow, analytical plan, methods of analysis and purchase of equipment. A quality control and quality assurance mechanism should be established to monitor the flow, entry, checking and validation of data. The importance of back

ups and their storage in a separate geographical location from the master computer was emphasized.

Monitoring, recording and reporting of adverse events are an important responsibility of the PI, but it is the duty of the sponsor through the clinical monitor and the investigator's brochure to ensure that the PI and research team understand the distinction between an adverse event (AE) and severe adverse event (SAE). The investigators need to be aware that there may be previously unobserved or undocumented adverse drug reactions or new trends in documented reactions, including diminishing rates of the previously reported ones. It was therefore emphasized that all AE's and SAEs must be documented and reported in a short-time frame, depending on the timing of reporting as indicated by the sponsor. It is the role of the clinical monitor to ensure that all systems set up for a trial are functional and are GCP/ICH compliant.

In keeping with the ethical requirements of safeguarding the trial participants from exposure to unreasonable or unnecessary risks, the establishment of a safety monitoring committee is essential. The safety monitoring committee assures protection of research subjects beyond what the IRB and ethics committee provide. The committee should comprise relevant experts to the trial, including but not limited to epidemiologists, biostatisticians, physicians, bioethicists and toxicologists. The safety monitoring committee must have an independent decision-making process and a decision-making flow-chart with clear go/no/go criteria established before the trial starts. It was pointed out that the committee may have no direct interaction with trial investigators, but should interact with IRBs or regulatory authorities. It was emphasized that should there be serious safety concerns with the trial product, the investigator must inform the IRB, which will in turn inform the safety monitors directly or through the sponsor.

In clinical trials, in order to ensure scientific rigorous hypothesis testing and generation of unbiased credible data, a randomised-controlled trial (RCT) is the gold standard. In this design a study participant is allocated to a group to receive a predetermined dose or regimen of a drug, placebo or intervention method in a blinded and controlled manner. The list or document, which contains the information indicating the group to which a participant is allocated, is referred to as the code. To maintain credibility the code must be kept strictly confidential and broken only following established SOPs which are clearly drawn up and available to all concerned parties at the beginning of the trial. In all phases of the clinical trial, investigators are blinded. It was emphasized that individual randomisation codes must only be broken and revealed to investigators, or the case of a medical emergency and serious events, to others who are responsible for managing the research participants. Every effort must be made to contact the local clinical monitor or sponsor before breaking of the code.

Group discussions focused on the benefits that the participants should expect from the research, researchers and sponsors as well as factors affecting voluntary and forced premature termination of a clinical trial. With respect to the benefits the participants should expect from the research, there was a consensus that the research participants should be compensated for their time and

travel costs. However, the compensation should not be of the kind that can influence or coerce individuals to participate. It was further agreed that, the community in which a product is tested should have free or subsidized access to the product if it proves to be beneficial. The benefit should also be extended to the general population where feasible. In case of injury or adverse reactions the research participant should be compensated to a level commensurate with the degree of injury. It was also agreed that an African voice is required in patenting of local drug formulations and in getting commercial benefits for communities whose local materials or indigenous knowledge are used in the development of pharmaceutical products.

With regard to voluntary and forced premature termination of the clinical trial, it was generally agreed that the community has a role because the reason for termination may be based on adverse events experienced by the participating individuals in the community. In addition to adverse events, a clinical trial may be terminated due to "acts of God" such as environmental changes as well as change in interest on the part of the sponsor, social-cultural factors and inability of the principal investigator to conduct the trial.

3. Ethical issues in Health Research

It was emphasised that the interests of research participants must always prevail over the interests of science and society. The four-bioethics principles of respect for persons, beneficence (maximize benefits and minimize harm), nonmaleficence (do no harm) and justice, must be strictly adhered to during conduct of trials. Reference was made to CIOMS Guidelines, particularly regarding to the rights of vulnerable groups such as children, prisoners, the mentally disabled, participants from low-income countries, pregnant women and breast-feeding mothers. From group discussions on the finding of a balance in science and ethics when designing clinical trials, it was agreed that trials with children, pregnant women and breastfeeding mothers, as participants must be discouraged unless the study has a direct bearing on these groups. The administration of placebo was deemed to be ethically wrong unless justified and when necessary the group that receives it must not be at a disadvantage.

The group and plenary discussions revolving on the issue of a signature following consent in the African context were very thought provoking. While there was a consensus that there is a role for collective and for spousal consent, there were diversified opinions on the issue of a signature for consent. In the final analysis this would depend on the locality, as there are communities from which signatures cannot be obtained, as members believe that their word is good enough. However, there are journals that require informed consent forms be signed and the PI must therefore find some solution if manuscripts are to be submitted to such journals.

4. Clinical and vaccine trials

Candidate malaria vaccines include sporozoite, liver-stage, asexual-stage and transmission blocking vaccines. These are evaluated on the basis of their location and function; their ability to induce an appropriate immune response as measured by in vitro assays; and the capability of such vaccines to reduce

parasitaemia threshold (malaria is defined as parasitaemia plus fever). Some of the current non-standardised in vitro assays are those that measure sporozoite and merozoite invasion inhibition (antibody-dependent cell inhibition – ADCI). Candidate malaria vaccines evaluated by the Afro-immunoassay network include MSP-1, MSP-3, (both merozoite surface proteins), BSF25 (liver stage), AMA-1 (rhoptry protein) and GLURP (soluble protein in the parasitophorous vacuole). The Afro-immunoassay multicentre project is a network sponsored by AMANET to validate antigen and immune responses in comparable studies done in different areas to obtain more conclusive data. The general objective of the network is to develop and introduce standardised immunological assays to measure immune responses.

Quality Assurance (QA) and Quality Control are very important in all trial studies because data generated must be accurate and credible. A suggestion for laboratories in the south to liaise and crosscheck results (internal monitoring and assurance) rather than depend on laboratories in the north was lauded as a good method of QA/QC.

The concepts of insurance and indemnity were examined owing to the widespread concern on the advocacy of protection of human research participants and the recent instances of serious or severe injuries. In some northern countries lawsuits have increased against investigators, institutional review boards, and academic institutions. Minimising risk in clinical research should be looked at in relationship with research participants, IRBs (strong IRBs are essentials since these look at the safety of participants), sponsors and government agencies. The following questions are important to consider:

- ◆ Do African researchers have insurance covers?
- ◆ Do African institutions have measures to protect trial participants and researchers from trial-related injuries?
- ◆ Are research participants aware of the risks involved in trials and how much risk are they willing to take?

Group discussion focused on dissemination of information. The PI is expected to keep the participants well informed about all aspects of the study. The community should also be informed on the background of the study and the reason for selecting the site for the study. The PI should make sure that a memorandum of understanding is established between researchers and communities. Although communication is usually with the sponsor, decision and policy makers, as well as regulatory bodies must be involved at all stages of the study including before, during and at the completion. Such information from the PI to the sponsor should include proof of competence of the PI to adhere to the protocol, on-site personnel and the accounting system. A memorandum of understanding on the role of the sponsor in information release must be established from the start. The participant is the primary owner of data/information although this is not always respected. It was a consensus that interviews with lay press should be limited to avoid distortions, particularly in drug and vaccine trials. A press release in simple language signed by the PI is more advisable.

5. Research applications and community follow-up

A presentation on public- versus private-sponsored research in an African context addressed funding of basic research on malaria vaccines providing lists of funding bodies and stages of clinical trials funded by these bodies. Safety was emphasized as being of prime importance in vaccine development process. Awareness of interests of the industry in vaccines that are most profitable, led to the ethical issue of African institutions' involvement in testing vaccines that benefit tourists rather than vulnerable groups such as under fives and pregnant women living in malaria-endemic areas. It was pointed out that conflicts of interest could greatly influence national policies. Both industry and researchers need to strike a balance on the issue.

Dissemination of research findings should focus on relevant data related to the actual plan of the study and the actual outcome assessed from the target population. To achieve this, the impact of the intervention should be assessed by referring to external sources of information related to the subject matter, comparing the existing information and the research outcome to show that the intervention made a difference. Evaluation errors in interpreting whether the intervention had an impact must consider three elements namely the changes brought by project; the outside influences such as changes in government, climate, trend, etc; and decline in interest of the research project. As far as publications are concerned, quality as measured by impact factor is more important than quantity.

There are four important areas that define authorship namely involvement in the proposal write-up, conduct of research, analysis of data and writing. The principal author must be involved in all these four processes. Authorship carries responsibility and authors must be able to defend the paper at anytime.

Responsibilities of the PI and sponsors to the stakeholders do not end when a trial is over. One of the major concerns is that quite often the health problem remains when the research is over. If the research is successful and the trial product proven to be effective some benefit must be awarded to the research participants, the community and particularly to the control group, which is often neglected. In cases where a product is not available for distribution the PI has the responsibility to at least provide information on the outcome and findings to all stakeholders. This information must be kept simple and straightforward. All documents related to the trial must be appropriately filed and archived. Both the final scientific and financial reports must be submitted to the sponsor.

Furthermore, right from the conception of a trial, it is important to have a clear vision on how funds will be generated to sustain the developed infrastructure and maintain the acquired equipment beyond the duration of the project.

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**THE FOURTH AMANET BIENNIAL
CONFERENCE**
**24-26 February 2004, Mount Meru Hotel, Arusha,
Tanzania**

AMANET announces the Fourth AMANET Biennial Conference that will be held from 24th to 26th February 2004 in Arusha, Tanzania. The theme of the conference is: **EXPERIENCES IN ORGANISING CLINICAL TRIALS IN AFRICA: THE ACCOMPLISHMENTS**. The conference will be held under the following sub-themes:

- Candidate antimalarial drugs in pre-clinical development
- Candidate malaria vaccines in pre-clinical development
- cGMP production of candidate drugs and vaccines
- African experiences on site characterisation for malaria intervention trials
- Capacity strengthening for the development of malaria interventions
- Clinical trials of antimalarial drugs
- Trials of asexual stage candidate vaccines
- Trials of pre-erythrocytic candidate vaccines
- Trials of transmission blocking candidate vaccines
- Lessons from vector control trials

At the conference, awards in the form of USD 1000, a memory stick and a certificate will be presented to each of the top three presentations from young African scientists. Extended deadline for submission of abstracts in 31 January 2004.

For further information on the conference and social events, abstract forms and online pre-registration, visit our website at:

<http://www.amanet-trust.org>

**AMANET WORKSHOP ON GOOD CLINICAL
PRACTICE FOR AFRICAN MONITORS**
April 2004

AMANET will hold a training workshop on good clinical practice for African physicians and scientists who are working in health research and training institutions and are interested in monitoring malaria intervention trials in Africa. Applicants must be middle or senior level investigators with proven experience in carrying out clinical trials. For further details and online application, please visit our website.