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## AFRICAN MALARIA NETWORK TRUST

### Training on ICH-GCP for Clinical Investigators Focusing on HIV/AIDS and Malaria Vaccine Trials

25-29 April 2005, Zanzibar, Tanzania

### Workshop Report

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#### Introduction

The WHO Initiative for Vaccine Research (IVR) in collaboration with AMANET and African AIDS Vaccine Programme (AAVP) hosted a five-day Training Workshop on “International Conference on Harmonization (ICH) of Good Clinical Practice (GCP) for Clinical Investigators Focusing on HIV/AIDS and Malaria Vaccine Trials” in Zanzibar, Tanzania from 25-29 April 2005. The 31 Participants were drawn from Botswana, Burkina Faso, Ethiopia, Gabon, Ghana, Kenya, Mali, Sudan, Tanzania, Uganda, Zambia and Zimbabwe. Facilitators came from WHO-TDR, WHO-IVR, AMANET and AAVP.

The aim of the workshop was to acquaint participants with:

- The roles and responsibilities of investigators doing research according to ICH-GCP standards;
- Current international ethical/regulatory guidelines for clinical research ;
- Requirements for HIV/AIDS and Malaria clinical studies;
- Developing of field Standard Operating Procedures (SOP's) and;
- Basics of data management and documentation skills.

Hon. Mussa Ame Silima, Zanzibar Minister for Trade, Industry, Marketing & Tourism, officially opened the workshop by pointing out that malaria is Africa's public health enemy number one, and the situation is deteriorating despite intensified efforts at containing it. As if that were not enough, the plague of the HIV infection and its deadly consequence, AIDS, is haunting Africa, especially in the sub-Saharan region where it is claiming many lives daily. The challenges facing Africa are real and require adopting workable strategies. The aim should be at training scientists so that they are empowered to actively participate in setting the research agenda for Africa, and contribute to development of appropriate intervention tools.

#### Overview of product development and principles of GCP

The development of a new drug or vaccine can be summarized into 3 stages: (i) Target discovery when a gene or protein link is found; (ii) drug discovery and (iii) development which includes pre-clinical testing and clinical trials in humans.

The primary aim of Good Clinical Practice (GCP) is to produce credible data in research while protecting the dignity and safety of trial participants.

GCP is an international ethical and scientific quality standard for the designing, conducting, recording and reporting trials that involve participation of human subjects. International Conference on Harmonisation (ICH) guidelines for GCP gives a set of international recommendations on the harmonised requirements for drug registration. They should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The basic principles of GCP ensure that the rights, safety and well-being of trial subjects prevail over the interest of science and society. The second basic principle is to have credible trial data and by following GCP guidelines, one ensures that data is accurate and verifiable.

### **Regulatory Authorities**

National Regulatory authorities have a key role to play in protecting subjects in clinical trials. They oversee the importation and use of the investigational product. In developing countries especially Africa, regulatory authorities are only now beginning to be familiar with their role in clinical trials. In many countries there are no regulatory authorities, and where they exist, often do not have regulations regarding clinical trials. The Tanzanian Food and Drug Authority was presented as a case for the role of regulatory authorities in Africa. The process and requirements of clinical trial drug importation was presented and practical implications for the investigators discussed. It was learnt that the regulatory authorities within the Eastern and Southern African region are in the process of harmonising their requirements as per ICH.

The need to work with and comply with regulatory authorities is cardinal in product development as they hold the key to the registration and public use of the product.

### **The Role of a sponsor**

During the workshop, the definition and responsibilities of a sponsor was clearly outlined. A sponsor was described as a person or institution who takes the responsibility for initiation, management and financing of a clinical trial. A financier may not necessarily be a sponsor if his/her interests do not go beyond that of philanthropy. It is the sponsor's responsibility to select the appropriate site, to appoint a qualified investigator, to delegate other roles outlined in the protocol and to provide the investigational product and all the information pertaining to it.

The sponsor should also be committed to providing indemnity to the investigator and compensation of the trial participants in case of a trial related injury. Overall, the sponsor should ensure that the trial is conducted in accordance with sound scientific principles and good clinical practice standards and that the operations are within existing legal and regulatory bounds.

### **Investigator responsibilities**

For this topic, participants were allocated the various responsibilities to present with practical examples from their own experiences. An investigator was defined as the person responsible for the conduct of the clinical trial at the trial site. S/he plays an important role from the initiation of the study till the end. Sufficient time and availability during the trial was emphasized. Adequate knowledge of GCP and understanding of the SOPs by the

investigator and his team is essential. The investigator should ensure adherence to the SOPs, communication with the community as well as safety of participants. Recruitment and enrolment of participants should be according to the protocol.

Case report forms completion should be done by the investigator immediately so that errors can be identified and rectified as soon as possible. Source documents should be kept by the investigator and confidentiality maintained.

Drug accountability with emphasis on storage, labelling, prescription should be followed as per protocol. While labelling is a sponsor responsibility, the investigator must ensure that storage or the cold chain is maintained as stated in the investigator's brochure. The personnel handling drugs should be qualified and trained for the job and proper accountability kept.

Essential documents were listed and said to individually or together allow the clinical trial to be complying to the Institutional Review Board. These should be filed and be readily available. They include investigator's brochure, study protocol, informed consent, patients information sheet, signed agreements between the investigator and sponsor, approval from the IEC/IRB, CVs of the investigators, signed, dated and completed CRF, administrative and communications with the sponsors to mention some.

### **Monitor responsibilities**

Monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that is conducted, recorded and reported in accordance with the protocol, SOPs, GCP and applicable regulatory requirements. Monitoring of a trial is a sponsor responsibility, but while the monitor is the eyes and ears of the sponsor, the monitor is also there to help the investigator and ensure the success of the trial.

The monitor is not there only to fault find but he is also there to identify sources of errors that may not have been apparent to the investigator and suggest solutions in order to ensure that trial data are credible. In order to achieve this, monitors must be appropriately trained and should have the scientific and / or clinical knowledge needed to monitor the scientific trial adequately.

The extent and nature of monitoring is determined by the sponsor and is commensurate with the level of technical detail involved.

The trial monitoring is an integral component of trial quality assurance process and critical for GCP fulfilment.

### **Role of the Institutional Review Board (IRB) or Independent Ethics Committee (IEC)**

An overview of ethics in research was given where participants were given the history of ethics in clinical trials with classical examples such as the thalidomide tragedy, the Tuskegee study, the Nuremberg doctors' trial of 1946. Declarations such as the World

Medical Association's Helsinki Declaration, CIOMS and others currently provide acceptable guidelines on health research ethics.

The role of the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) is to provide guidance, public assurance in protecting the rights, dignity and well-being of the trial participants. To do this an IRB/IEC needs to be competent in its composition and operations. Unfortunately, most IRBs in Africa are still struggling to attain that level of proficiency, and therefore, investigators must participate in ensuring that their IRBs are up to date with current issues relating to biomedical research.

The informed consent process as well as confidentiality was emphasized as a critical responsibility of the IRB. The IRB should not simply provide initial approval, but still has responsibility to monitor the progress of the study to ensure that the ethical principles are being kept.

The investigators are expected to know the SOPs of their IRB so that their protocols are considerate of the local ethical requirements. Issues to do with the study design, randomisation, placebo use, investigational procedures must be evaluated and approved by the IRB before a study can start. During the conduct of the trial, serious adverse events, site monitoring reports, safety monitoring board reports should be continuously reviewed commensurate with the degree of risk to trial participants.

### **The Voluntary informed consent**

Over the years, guidelines on voluntary informed consent have evolved to what they are now, unfortunately, after a number of gross misdeeds. Good clinical practice dictates that a potential subject is provided with adequate information about the conduct of a study, the potential benefits, risks and discomfort that participation may entail. The participant must be made aware of his or her right to abstain and to withdraw before actual completion of the study without reprisal. And they must be given enough time to make their decision.

It is the responsibility of the investigator to ensure that the participant has understood the information for which a freely given consent is being obtained in writing. In case it cannot be obtained in writing, this should be witnessed and appropriately documented. Prevailing conditions such as the laws of a country and the cultural practices of the study population should always be taken into consideration.

### **Safety Issues**

Safety of trial participants is paramount and an important consideration in clinical trial research irrespective of the trial Phase. Although preclinical and clinical data of a product is carefully collected, it does not always reveal all possible side or adverse effects. Many adverse reactions are revealed only when the product has been used by a large number of people. The Investigator must also have a good knowledge of what adverse events and serious adverse events are, and the criteria (per protocol) on deciding causality. Investigators have a moral and ethical obligation to be thorough with safety issues.

### **Principles of GLP and GCP compliant laboratory**

Historically Good Laboratory Practice (GLP) principles were conceived as a result of irregularities and sometimes fraud committed in research and even industry laboratories, resulting in the Kennedy hearings on New Drug Applications and proposed regulations on GLP (FDA 1976; 21 CFR 58 1979). The aim of GLP is to produce quality data that is credible and verifiable. The principles of GLP and GCP are complimentary to each other. The Organization of Economic Cooperation Development (OECD) defines principles of GLP as “quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported”. The purpose of the principles of GLP are to promote the development of quality test data, to ensure that studies are reliable and can be trusted, conclusions reported are verifiable and data can be traced. A laboratory supporting GCP clinical trials ought to abide by the basic principles of GLP.

### **Quality assurance and quality control**

Quality assurance (QA) is defined as all those planned and systemic actions that are established to ensure that the trial is performed and data are generated, documented (recorded), and reported in compliance with good clinical practice and the applicable regulatory requirement(s) (ICH GCP 1.46).

Quality control (QC) is the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled (ICH GCP 1.47). The importance and purpose of QC and QA is to ensure that what is conducted and data generated, documented is reported in compliance with the protocol, GCP and the applicable regulatory requirements. It is the responsibility of the sponsor to ensure that QA and QC are implemented and maintained. The roles of the sponsor, investigators, IEC and regulatory bodies were outlined.

Trial auditing was discussed under this theme and it was defined as a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and data were recorded, analyzed and accurately reported according to the protocol, sponsor’s standard operating procedures (SOPs), good clinical practice (GCP) and the applicable regulatory requirements (ICH GCP 1.6).

It was emphasized that auditing is part of implementing quality assurance and it is independent of and separate from routine monitoring or quality control functions. The sponsor’s audit visit assures that subjects’ rights and welfare are being adequately protected, helps to identify and correct problem areas and provide suggestions to improve performance. Common monitor and audit findings including protocol non-compliance, inadequate source documents, inadequate investigational products records and informed consent issues were discussed.

### **Standard Operating Procedures**

Participants were taken through a discourse on preparation of standard operating procedures. Characteristics, elements and format of a good SOP were presented and case studies were given for which the participants had to write their own SOP's as practical exercises. The various topics that arose from participants confirmed that SOPs should be written on all procedures in a clinical trial and that there was no limit to the number of SOPs one could have. The ultimate goal of an SOP is to provide clear and easy instructions on trial related procedures.

### **Overview on data management and statistics in clinical trials**

One of the basic principles of GCP is to produce credible clinical trial data. Data collected in clinical trials are paramount for deciding whether a given trial should proceed to the next phase, and also for regulatory authorities for making decisions on product approval. Hence the data must be managed in compliance with all applicable regulatory requirements and with utmost care.

The basic principles of clinical data management cover the study protocol itself, design of case report forms (CRF), design of clinical trials database and programming, data acquisition and entry into this database, data review, validation, coding, and database finalization and closure. Then the data can be sent for statistical analysis and reporting.

Participants were taken also through the process of developing statistical analysis plans where sample size considerations, analytical plans for the data and how to handle dropouts and missing data discussed. Statistical analysis should be planned before the start of the study. It was emphasised that a type 1 error was more serious if committed. The use of a 95% confidence interval was said to give a much more data information than p-values alone.

Handling of dropouts was discussed and it was emphasised that once a participant is randomised he/she has to be included in the analysis. Exclusion can lead to biased results, as the magnitude and direction are unknown. Missing data can lead to biased estimates, incorrect estimation of variance and changing may reduce the sampled population. It is important to note the pattern of missing data and the mechanism that is which data is missing? Who is missing data? Is the data missing completely at random (MCAR)? Or missing at random (MAR)? Or it is missing not at random (MNAR)? The Data Manager and Statistician must be involved right from the beginning of plans for the study.