



Second Training Workshop on Good Clinical Practice (GCP) for Clinical Investigators organized by the INDEPTH Network, the Malaria Clinical Trials Alliance (MCTA) and the African Malaria Network Trust (AMANET)

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Introduction

The INDEPTH/MCTA network in collaboration with the African Malaria Network Trust (AMANET) organized a five-day workshop on Good Clinical Practice (GCP) on 6-11 November 2006 at the KEMRI-Wellcome Research Programme, Kilifi, Kenya. This was a second GCP workshop organized by the mentioned parties in 2006. The first GCP workshop was organized in August 2006. A total of 27 participants and 10 facilitators from Burkina Faso, France, Gabon, Ghana, Kenya, Malawi, Nigeria, Senegal, Tanzania, The Gambia and Uganda attended the workshop.

Day 1

The workshop was officially opened by Dr Norbert Peshu, Kenya Medical Research Institute (KEMRI) Director for the Centre for Geographic Medicine Research (CGM) Coast. After welcoming all the participants he emphasized the importance of Good Clinical Practice (GCP) training for clinical investigators especially in Africa. He also thanked the organizers for choosing Kilifi for the training. He closed his brief remarks by assuring all the participants that they will be accorded all the necessary help while in Kilifi.

The opening ceremony was followed by a speech from the INDEPTH Deputy Director Dr Osman Sankoh who started by giving a brief background of INDEPTH activities, and the various sites with a demographic surveillance system (DSS) participating in the INDEPTH network. Dr Sankoh also talked about the new initiative at INDEPTH; the Malaria Clinical Trials Alliance (MCTA). He said that MCTA objective is to facilitate site preparation for the effective conduct of clinical trials for life-saving malaria interventions and simultaneously promote the long-term development and sustainability of clinical trial sites in resource-constrained countries in the developing world.

The first lecture for the day was given by Dr Roma Chilengi on “Good Clinical Practice (GCP): A historical perspective”. Dr Chilengi took the participants through the historical events which lead to the need for GCP. He elaborated meetings and reasons leading to the formation of the International Conference on Harmonization (ICH) in 1990. The Definition of GCP was also presented as an international ethical and scientific quality standard, for designing, conducting,

recording and reporting trials that involve participation of human subjects. It was noted that some countries have their own versions of GCP standards. This raised a question from one of the participants whether Africa should also come up with her own version of GCP. This was seen to be quite in order as the diseases affecting Africa are quite different with those seen elsewhere. The Challenge remained.

The next session was on “*Steps in drug development*”, also presented by Dr Chilengi. In this talk, participants were taken through different phases of drug development pipeline. Drug development was said to involve two major steps; Research and Development, and that the whole process; from concept formulation, preclinical research, clinical research, regulatory authority review to licensure and marketing can take up to 20 plus to completion.

The session after lunch was opened by Dr Ally Olotu who spoke on “*Who is a sponsor?*” In this lecture, Dr Olotu defined who is a sponsor and the various responsibilities attached to him/her which include among others development of the trial protocol, preparation of standard operating procedures (SOPs), product liability, clinical trial insurance, providing study information, selection of sites, and handling of data and reports.

The next session was facilitated by Dr Nditonda Chukilizo who discussed “*the role of Regulatory Authorities*”. Regulatory Authorities (RAs) were said to be institutions which are empowered either by governments or international bodies to regulate trade or conduct in medicine and clinical trials. These authorities are also referred as Medicine (Drug) Regulatory Authorities (MRAs). Dr Chukilizo gave a well detailed outline on the roles of MRAs, and also eluded on the obligation of the principal investigators to the former. He concluded by enumerating on the challenges facing MRAs.

The last talk for the day was given by Dr Mark Kaddu-mukasa on “*Investigator and His/Her responsibilities*”. Dr Kaddu-mukasa discussed the qualities of a good investigator. He also enumerated various responsibilities of an investigator in a clinical trial.

In summary the day ended well and the facilitators did an excellent job, the manner each presented their area showed they were well acquainted with their subjects. The content of presentations was also excellent. There was also active participation from the participants, either by way of asking question or through sharing of experiences. All these made day one sessions very enchanting.

Day 2

Day two kicked off with the topic “*Role of Ethics Committees (ECs)*” presented by Dr Chilengi. This talk discussed roles of the ECs to hinge on the protection of the human participants in clinical trials. Dr Chilengi emphasized the basic requirements that make a trial ethical, this included value, scientific validity, fair subject selection, favourable risk benefit ratio, independent review, informed consent and respect for potential and enrolled subjects. Ethics committees need to operate in compliance with the currently set out international guidelines.

Dr Kaddu-mukasa then presented on “*the role of Data Safety Monitoring Boards (DSMBs)*”. He emphasized that DSMBs are independent monitoring committees even though they are usually established by the sponsor. Their main role is to review, evaluate and provide advice on regular basis. He also mentioned that a typical DSMB is usually made up of 2-3 medical experts in the field under study, a biostatistician and possibly, consultants from other specialties.

Dr Chilengi then took participants through “*Standard Operating Procedures (SOPs)*” in the next presentation. He started by stressing that SOPs are very vital and have to be written for everything related to the trial. He further explained that SOPs simplify the process of organization and documentation and at the same time maintain high standards of GCP. He also pointed that properly done SOPs could be used as training tools, improve efficiency, and allow for uniformity and transparency. SOPs were said to be prerequisite in GCP.

“*Quality Control (QC) and Quality Assurance (QA)*” was presented by Dr Hildur Blythman who stressed that QC is a continuous process of monitoring and reviewing the various operational units of a trial in accordance with the protocol, GCP and approved SOPs. QA was said to be an independent assessment of QC systems. Dr Blythman explained QA/QC systems as a continuous cycle of SOPs which progressively improve upon regular assessments and corrective measures.

Dr Ogutu then talked about “GCP Compliant Laboratories (GCPCL)”. He mentioned that the principal aim of a GCPCL is to ensure that analytical tests, reporting, interpretation and verification are accurate. He noted that this standard is based on good laboratory practice, a concept with a history akin to GCP. GCPCL requires that staff is adequately trained; SOPs are available for all procedures, a functional quality control and quality assurance is in place; equipment regularly maintenance, and sound record keeping. Like GCP, observing GCLP provides public assurance that trials results are credible.

The talk on “Clinical Data Management” was then given by Dr Abdunoor Mulokozi. He started by explaining that data is information collected for evidence. He further said that the role of data management in a clinical trial is to ensure proper recording, handling and storing of all data according to the study protocol to allow for accurate reporting.

The last presentation for the day was by Dr Ally Olotu on the topic “Trial logs”. Dr Olotu said that documentation in GCP forms the basis of verification and accountability. He then briefly outlined and explained the several types of logs used in a clinical trial.

Day 3

Dr Kaddu-mukasa made the first presentation for day three on “*Handling of study product*”. Dr Kaddu-mukasa said that a study product could be a drug, vaccine, medicinal products or a new investigational drug. He further explained that the sponsor supplies the investigator with the investigational product (IP). This is done only when the required document(s) like approval/favourable opinion from institutional review board (IRB)/regulatory authority (RA) are obtained. The investigator should ensure that written procedures are followed.

Dr Bernard Ogutu then gave a brief lecture on “*Authorized signatories and CRF completion*”. GCP requires a security system that prevents unauthorized access to data. Therefore, investigators should maintain a list of trained staff that is authorized to make data entries or changes in CRF’s. Examples of how to make corrections on the CRF were shown emphasizing the need for audit trail.

The workshop went further with a lecture delivered by Dr Abdunoor Mulokozi on “trial randomization and coding”. Randomization was said to be a process of assigning trial participants (subjects) to treatment or control group using an element of chance to determine the assignment in order to reduce/prevent bias. This method was said to allow each participant to have equal chance of being allocated to any of the trial. Dr Mulokozi said that “code” refers to a list or document which allocate a study participant to receive a drug/placebo/intervention in a predefined dose or regimen in a blinded trial. This is also referred to as “blind randomization”. A

proper SOP must be followed when breaking the code in case of a medical emergency or serious condition during the trial; all this has to be fully documented.

The presentation on “*Essential documents*” was given by Dr Phillips. Dr Phillips said that essential documents are purposely for filing, auditing and validation of trial conduct. These documents either individually or collectively allow for the evaluation of the conduct of the trial and the quality of data produced. He explained that filing of documents in sponsor and investigator sites always assist in the successful management and auditing of a trial.

A very enlightening discussion on “*when should a trial begin*” followed. General contribution was made by each of the participants. Participant suggestion before a trial begins included signing of contract agreement between the institution/investigation and sponsor, site assessment/pre-trial visit, review of protocol by investigator/IRB/regulatory authority, recruitment of staff/trial team, submission of budget, training of staff, soliciting final approval, public initiation, re-training of staff/personnel and proper agreement on time of monitoring visit must be confirmed before a trial begins.

The final presentation was on “*adverse events (AEs) and serious adverse events (SAEs)*” in clinical trials. This lecture was given by Dr Blythman who said that pharmacovigilance objectives are to detect, evaluate, understand and prevent the risks of adverse events of medication. She further said that “any untoward medical occurrence in a patient or clinical investigative subject, administered with a pharmaceutical product and which does not necessarily have a casual relationship with treatment” qualifies to be an adverse event. On the other hand, a serious adverse event (SAE) was said to be any untoward occurrence resulting in death, is life threatening, requiring hospitalization or prolongation of existing hospitalization, results in disability, incapacitation, or any that leads to congenital anomaly/birth defect. Dr Blythman further emphasized that all AEs must be recorded in CRF and SAEs must be documented and reported in to the sponsor within a specified short period i.e. 24-48hrs.

The participants then had the opportunity of touring the KEMRI-Kilifi facilities, guided by Dr Olotu. The participants were able to witness what it means by GCP, SOP and electronic CRF as implanted at the KEMRI Hospital. Participants also visited different departments of KEMRI research laboratories. The laboratories are well equipped and GLP compliance. The participants further toured Jungu village which is 30 km away from the centre, where a vaccine trial is to be conducted. The participants had a real-life encounter of what it means by preparation before a clinical trial and all other requirements. This was a great opportunity for the participants as they also interacted with the research community.

Day 4

The day started with Dr Blythman continuing the session on “*adverse events reporting*”. She emphasized that higher standards of safety is expected from the trial because product are to be administered to healthy individuals. Investigators are key in the reporting of adverse events as the sponsors and drug companies which developed the products are normally not in contact with patients. The critical issue is to have clear definitions and SOP’s on how to identify these events and how to establish causal relationship. The take home message was: *Primum non nocere* (first of all, do no harm- It is our moral duty to protect public health first! Clinical science should be secondary).

Then the “*role of a clinical monitor*” was taken by Dr Kaddu-mukasa. He defined monitoring as procedural activities which ensure quality assurance during a clinical trial. The clinical monitor is therefore said to be the “eyes and ears” of the sponsor i.e. link between the investigator and

sponsor to ensure quality patient care and quality data in the trial. On what is to be monitored, he said that everything in a trial is subject to monitoring. Another important area in monitoring was said to be the verification that written informed consent is obtained before each patient is enrolled in the trial.

Dr Kaddu-mukasa mentioned that the challenge in this process include arrangement and planning of monitoring visits which should be planned in such a way that the principal investigator and all required documents such as case report forms (CRFs) are available for clinical monitoring.

Dr Blythman came back to lead a discussion on “*data queries*”. She emphasized that in general, data are generated to provide information, enhance knowledge, to enable decision-making and to develop new products. Because of the tremendous amount of data from various sources from multiple protocols for a single product, a strong data management process is essential to provide a quality product. The purpose of queries was said to be that of being able to correct mistakes observed in the data.

Dr William Mwatu facilitated a discussion on “*informed consent process*”. He defined informed consent as a process by which a participant voluntarily confirms his or her participation in a particular trial, after having been informed of all aspects of the trial that are relevant to the participants to make informed decision. He emphasized that consenting should be a continuous process. Participation in a trial should be voluntary after information has been given on all aspects of the study and should be done in compliance with ethical standards. Dr Mwatu said that there should be no coercion or undue influence of the potential subject, no apparent waiving of subject rights or release of responsibility. It is important to note that the responsibility for proper consenting rests on the principal investigator.

The subject drew a lot of comments from participants during discussion time.

Group work

The session was followed by group work during which the participants groups took turns to identify shortfalls in a hypothetical information sheet and consent form. Participants demonstrated their grasp of the subject by giving an exhaustive critique on the flaws in the informed consent document.

Dr Mwatu later took another session on “*insurance and indemnity*”. He defined insurance as a guaranteed payment in the event of loss or injury while indemnity is security from damage or loss or injury or compensation for loss or injury. It is a GCP requirement for the sponsor to provide insurance and indemnify the investigator or institution against claims that arise from the trial and also for treatment costs of trial participants in the event of trial related injuries. He identified some of the risk areas for law suits such as recruitment and enrolment, informed consent process, adverse events, use of study data for other purposes other than that consented for and breach of confidentiality. Investigators should however note that sponsors have insurance to cover study participants for any injury incurred during a trial but they do not cover for negligence on the part of the principal investigator.

After lunch, Dr Mwatu facilitated a session on “*premature termination of a trial*”. He pointed out that a trial could be terminated prematurely due to safety, financial, or other unforeseen reasons by the investigator, sponsor or the ethics committee. In such a situation, all study participants should be promptly informed and every effort should be made to assure appropriate therapy and follow up of subjects.

This session was followed by that of a talk on “*Trial audits and inspection*”. In this presentation Dr Chukilizo defined a trial audit to be a systematic and independent examination of trial related activities and documents to determine whether evaluated trial related activities were conducted, and the data recorded, analyzed and accurately reported according to the protocol, standard operating procedures (SOPs) and applicable regulatory requirements. Trial audit was said to be part of quality assurance but independent and separate from routine monitoring or quality control functions. It was further said that an audit may be part of a routine as quality assurance or arranged in case of suspicion of non-compliance or retrospectively by regulatory authorities of archived records to verify compliance with GCP.

Day 5

The last day was opened by a presentation by Dr Mwatu who discussed “*study close-out issues*” emphasizing that researchers should respond to local needs of endemic areas and that they should comply with regulatory requirements. Then he went on and talked about capacity building where he emphasized that clinical researchers should promote sustainability and ensure full and active community participation in building capacity and infrastructure to ensure adequate health care facilities after the study is over. He mentioned that study close-out activities include continuity in follow ups of adverse events, SAE and pregnancy. Data queries need to be resolved quickly, investigational products should be returned or destroyed, ethics committees should be notified of the end of study and clinical study report should be written. He concluded by saying that governments should support research agendas by ensuring that regulations and guidelines on the conduct of trials are well articulated.

In a presentation on “*Reports*” by Dr Chilengi, said that reporting is the act of providing information or data to another party. He emphasized that the investigator should ensure accuracy, completeness, legibility and timeliness of data reported to the sponsor in the CRFs and in all required reporting.

The last talk was on “*Participants and research community*” by Dr Chukilizo who discussed issues on GCP products, accountability, audit certificates, final monitoring reports and document retention. He went further and elaborated on what needs to be done when the trial is completed, emphasizing on the role of the principle investigator, monitor and sponsor. The presentation further discussed international guidelines on provision of health care when the trial is over. He concluded that since experimental products are not often made available after trial, some activists object to their testing in poor communities. The take home message was that benefits of the participants have been neglected and that this should be given the attention it rightly deserves.

After this presentation, participants sat for a Post-course evaluation, which was followed by awarding of certificates and closing remarks by Dr Norbert Peshu and by Prof Charles Newton.