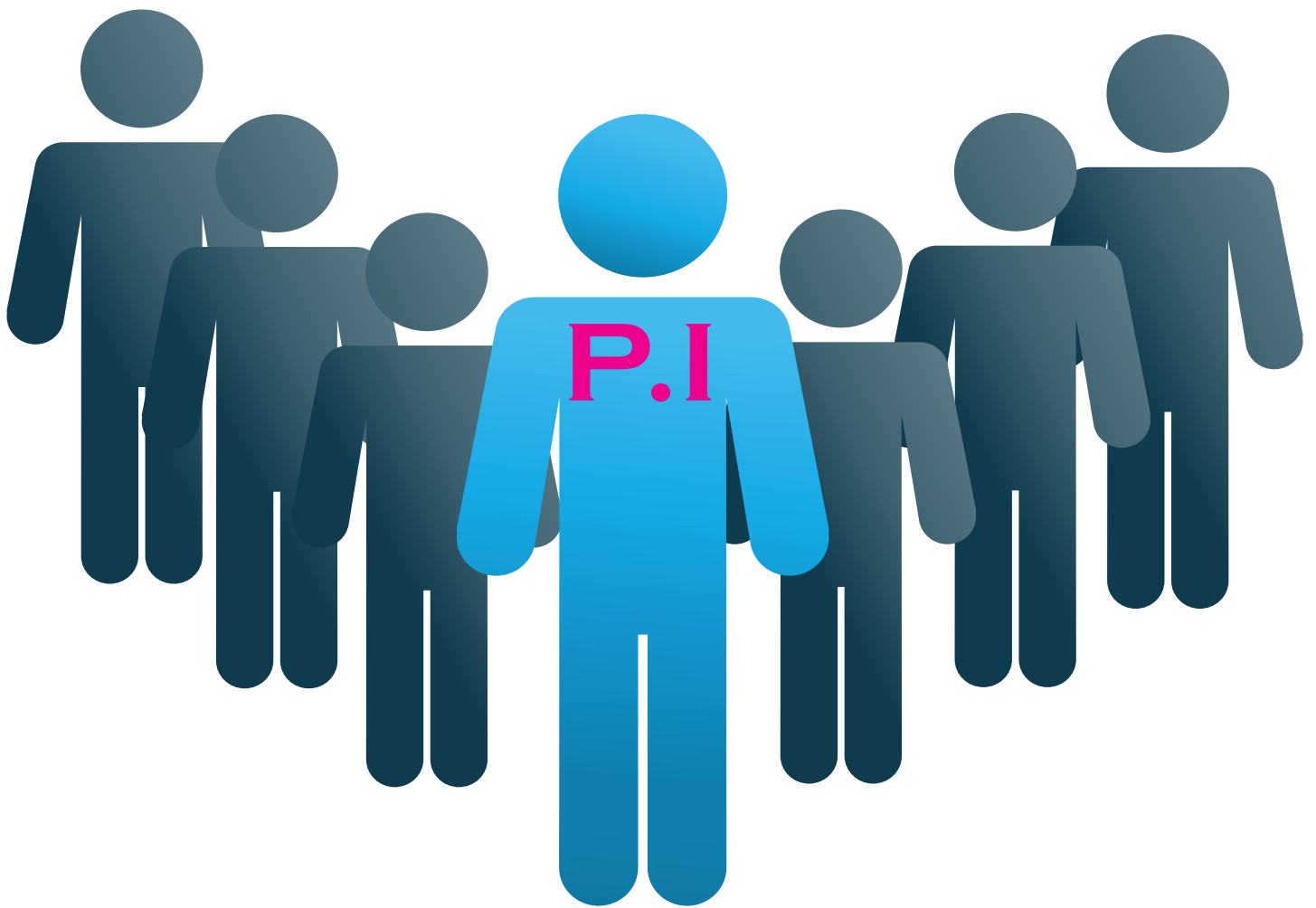


KEMRI Bioethics *Review*

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The roles of a Principal Investigator in research

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From the Chief Editor

Prof Elizabeth Bukusi

I am glad to present to you our final issue of the sixth volume of the KEMRI Bioethics newsletter. In this issue we focus on the roles of a principal investigators in research. The title of a Principal Investigator (PI) is a sought after, respected but also hugely demanding role for any scientist/researcher. Being a principal investigator comes with unique responsibilities; the primary role being ensuring that the project is completed and achieves its goals and objectives with the regulations and administrative requirements. In striving to achieve project goals and objectives, PIs have to balance time and effort dedicated towards the many tasks at the plate of a PI which include ensuring compliance with the research and financial regulations, supervising staff and project activities, responding to queries from funding agencies as well finding time to attend to scientific responsibilities like writing abstracts for conferences, manuscript development and attending scientific meetings. And of course there is always the next grant application to start working on.

Among the activities that ensure smooth operations in a research project is compliance to scientific and ethics regulatory affairs. It is ultimately the responsibility of the PI to ensure that a project is implemented according to the approved protocol and in compliance with existing regulations set out by the institutions, the funding agencies/sponsors or internationally recognized standards. The PI must therefore be well versed with local and international scientific and ethical guidelines and other research guidelines that govern their field of research.

In this issue, a team from the SERU secretariat define who a PI is and his/her roles. The secretariat staff also highlight the procedure of changing a PI as per the KEMRI regulatory system. We also share excerpts on the roles of investigators as outlined by some international research guidelines which KEMRI subscribes to. We hope you enjoy the reading.

Let me take this opportunity to wish you every blessing during the Christmas season, a peaceful end to 2016 and prosperity and good health for 2017.

Editor in Chief.

The **KEMRI Bioethics Newsletter** is published every 3 months and hosted on the KEMRI website. We publish articles by KEMRI affiliated authors and from other contributors from all over Kenya. The scope of articles ranges from ethical issues in biomedical science, healthcare, technology, law , religion and policy.

The chief editor encourages submission of articles as a way of creating awareness and discussions on bioethics

[please write to ddrt@kemri.org](mailto:ddrt@kemri.org)

A word from the Ag Director, KEMRI

Dr Gerald M.Mkoji



The Principal Investigator (PI) is an individual entrusted with authority and responsibility to direct the project or program supported by a grant. Being a principal investigator is a huge responsibility that demands previous experience in being part of a research project or a leading a research project.

Principal investigators are the leaders of the research for health studies whose objective is to generate scientific evidence which could lead to detecting, treating and/ or preventing disease. The role of a PI starts with the generating of a scientific idea which can be written up and submitted for funding and becomes realized when the funding is made available for the project to be implemented.

A KEMRI PI is duty bound to ensure that a study is conducted according to the approved protocol and in compliance with the Institute's and national regulations and any other regulations that may be applicable. The PI is also in charge of protecting the rights, safety, and welfare of human subjects under the investigator's care, in projects where human subjects are involved. The protection of research human subjects is an area in which KEMRI has been keen on for the last few years, owing to the increasing number of clinical trials conducted in the country. We have managed to restructure our research regulatory system by setting up the Scientific and Ethics Review Unit with changes that have not only improved the review turnaround time, but also, strengthened the review capacity of the Committees in order to guarantee the safety of research participants, and to keep track of reported adverse events during the conduct of research.

Safety reporting is another key aspect of our reg-

Ethical conduct and protection of human subjects is a must for validity of research, I therefore urge PIs to take seriously the role of ensuring subjects are protected and that research is conducted in an ethical manner by complying with regulations and guidelines.

ulatory system that we want to improve due to the rising number of clinical related research conducted by KEMRI PI's, and once fully realized, the KEMRI SERU will be able to support in the monitoring aspects of clinical trials and also undertake audits when needed.

Ethical conduct and protection of human subjects is a must for validity of research, I therefore urge PIs to take seriously the role of ensuring subjects are protected and that research is conducted in an ethical manner by complying with regulations and guidelines.

As we continue to work towards 'better health' for those we serve, let us ensure that we continue to uphold the basic principles that ensure that the right of every participant is upheld as is expected by our constitution. Let me wish you all a Happy Christmas and the best of 2017 as we continue to work towards improving lives globally through research.

Gerald M. Mkoji
Ag Director
KEMRI

A word from the Ag Deputy Director, Research and Development



Dr Evans Amukoye

Welcome to this issue on the roles of a Principal Investigator (PI) in research. A PI has the overall responsibility of ensuring the scientific and ethical conduct of the research study. This includes protecting human subjects' rights, safety and welfare, protocol compliance, and adherence to institutional, national and where applicable international regulations and guidance.

The role of a PI is a huge task that requires a one to be at the "top of the game" throughout the project period. Responsibilities cut across financial decision making, human resource management, getting involved in field operations and also handling and responding to queries from various regulators and funders. These responsibilities can be overwhelming and time management is of critical importance. This is true especially if one is the PI for more than one project being implemented at the same time. It can be possible that one ends up spending more time on one aspect of a project while neglecting others. Some

The role of a PI is a huge task that requires a one to be at the "top of the game" throughout the project period. Responsibilities cut across financial decision making, human resource management, getting involved in field operations and also handling and responding to queries from various regulators and funders

logistical aspects can also be quite complex especially in clinical trials e.g procurement, storage and distribution of investigational products e.g drugs, this may require a significant portion of a PI's time. While delegation to the appropriate staff members who are fully qualified and trained is usual, the PI is still the one who is held accountable. Other key operational aspects which include logistical, financial or HR matters are not matters in which scientist are routinely trained during post graduate studies. And the ten-

dency is that one learns on the job as one implements research from the smaller studies one may conduct during graduate school, to the larger studies which may be multi institutional or even multinational. For the success of any specific project, the PI must find a healthy balance in handling all these responsibilities.

The cycle of research is a never ending one, as one cannot wait for one study to completely close out before the next one starts. And ensuring that one is able to mentor the next generation of PI's is critical to expanding the research portfolio and mandate.

The secret in part for successfully managing responsibilities as a PI is learning and utilizing the art of delegation of duties. Many of the roles can be delegated by a PI and for this there has to be an adequate budget or adequate staff available to be in charge of certain study roles. This strategy enables a PI create time to effectively be involved in all aspects in more supervisory role. Delegation demands supervision; the PIs should commit to adequately supervise study staff to ensure compliance to the protocol.

Having served as PI for many studies in my many years of research, and having had multiple studies running concurrently, I cannot over emphasize the need for dedicated teamwork, and mentoring as a key to success.

The cycle of research is a never ending one, as one cannot wait for one study to completely close out before the next one starts. And ensuring that one is able to mentor the next generation of PI's is critical to expanding the research portfolio and mandate. I hope that those who are PI's, those who work with a PI and those who aspire to be PI's will find this newsletter informative.

Merry Christmas and a Happy New year.



DEFINATION AND ROLES OF A PRINCIPAL INVESTIGATOR (PI) IN RESEARCH

By Mariam Macharia, Gideon Cornel Msee, and Papias Mwangi (ARO's SERU).

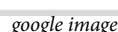
We live in an ever evolving and sophisticated world where we are the leaders, managers and implementers of some of the very intricate systems and projects. These systems are part and parcel of our daily lives and therefore we should be knowledgeable and adept to the level of the sophisticated and complex systems.

A pilot for instance must prepare carefully before taking off by ensuring instruments, flight controls, and the engines are working properly. Pilots additionally talk with tower administrators about climate conditions preceding flight. When they have weather forecast information, they use it to select a safe altitude, velocity, and flight course. If a plane is flying in severe conditions, diminishing visibility, pilots must depend on their

instruments to fly with help from aviation authority technicians. The most troublesome undertaking for pilots is taking off and landing. The two aspects of piloting require a joint effort between the pilot and co-pilot. It also calls for the pilots to be well trained and skilled professionals.

A Principal Investigator (PI) "manages" a similarly intricate and sophisticated system of an investigation just like pilots, only that the intricate and complicated system is a research project and not flying an aircraft. Research is universally defined as a systematic investigation developed to contribute to generalized knowledge. Being a systematic undertaking, research like flying a plane can be intricate, and for this reason, researchers or PIs need proper training and experience. This

In Research, the PI is in direct contact with participants more than the funders and other stakeholders in a research project. The PI takes direct responsibility for completion of a research project, including designing, directing, implementing the research and reporting directly to the relevant stakeholders of the research. A human subject or participant is a living individual about whom a researcher acquires the research data. Every research protocol must have an assigned PI who oversees the proper scientific design of the research protocol, study implementation, appropriate data collection, and recording. It is the role of a PI to ensure compliance with regulatory and ethical obligations regarding the use of human subjects in research and that informed consent procedures and prerequisites are achieved. Additionally, the PI must adhere to the reporting requirements of the Institutional Review Board (IRB), the study sponsor, and other relevant research stakeholders. Some important research regulations and regulatory bodies exist for which a PI depending on where and how the study is conducted, should be acquainted and conform. These regulatory bodies and research regulations include the Council for International Organizations of Medical Sciences (CIOMS), World Health Organization (WHO), Belmont Report, Declaration of Helsinki, 45 CFR 46, and Office of Human Research Protections (OHRP).



Subject Selection: PI should develop a sound and well written protocol with appropriate subject selection and justification for exclusion of any class of subjects. The protocol should outline the protection of subjects from potentially un-

necessary or harmful exposure and avoids selection bias. The PI is ultimately responsible for ensuring that any foreseeable risks are weighed against the benefits and that the benefits outweigh the risks. It is for the PI to ensure that any known risks are minimized to the maximum extent possible.

Informed Consent (IC) and Informed Assent (IS):

It is the PI's responsibility to ascertain that the critical component of human subject's protection which is to provide comprehensive, clear and easy-to-understand information about a protocol is available to a subject or their Legally Authorized Representative (LAR). Assent is also essential for minors or adults unable to provide consent, who can comprehend the concept of research. Subjects or their LAR should freely give Consent/Assent before participation in any research activities.

Confidentiality: Research data confidentiality should be maintained to protect subjects from



any potential harm. An Investigator needs to obtain a certificate of confidentiality when collecting sensitive information that might pose a risk to study subjects.

Safety Monitoring/Reporting: A PI should ensure that a well-designed safety monitoring plan and prompt reporting is created in order to protect subjects in case of any unanticipated

problems.

Project close out and continuous review reporting: A PI should ascertain that the research complies with technical, progress, and compliance reporting requirements of an IRB's research regulations, policies and procedures. This is achieved through timely submission of annual renewal and study closeout documents to the relevant IRB for review and approval.

Publication: It is the role of the PI to disseminate any important scientific information resulting from the research to the society as well as the participating subjects.

A Co-Investigator (CO-PI)

A Co-Investigator (Co-PI) is an individual who makes a significant contribution to a project. The PI relies on the Co-PI to assume his/her responsibilities whenever called to do so. It is common practice to allocate specific aspects of a project to Co-PIs e.g research regulatory activities, finance, and procurement of investigational products e.t.c. Each person with a role in the project can be included in the proposal and on project documentation as a Co-PI provided the sponsor accepts this role.

History of research guidelines and ways Principal Investigators adhere to them.

Prior to the Pure Food and Drug Act of 1906, there were no consumer regulations. Food and Drug Administration (FDA), Common Rule and Institutional Review Board (IRB) did not exist. After the enactment and creation of the Food and Drug Administration, governments felt the need to develop regulations that would govern use of humans in research.

The need to develop human research guidelines that would protect human subjects was precipitated by historical atrocities. The first international document was the Nuremberg code of

1948. This document introduced the concept of “voluntary consent and informed consent.” It was precipitated by the abhorrent and tortuous experiments carried out on Nazi prisoners during World War II. The prisoners were subjected to a series of experiments some of which included being put under extreme temperatures and altitudes to observe the physiologic response of the body. The experiments left most of the prisoners dead or permanently crippled. It was the American military tribunal of December 9, 1964, that formulated the code to prosecute the 10 German Doctors. The document contained ten guidelines most important is that participation in any study should be voluntary i.e. Participants must be informed and they should voluntarily make the decision to participate and also to withdraw at any time from a study. The research benefits and risks ratio of participation should also be favorable.

The Tuskegee study of between 1932 and 1972 which involved low-income African-American men, four hundred (400) of whom were infected with syphilis was also another earthquake that led to the drafting of ethical guidelines. The study saw the men receive free medical examination but information on them being infected with syphilis and the cure (penicillin) discovered in the 1950s was withheld. The men thought they were being treated for “bad blood”. Many subjects died of the disease. The study was stopped in 1973 by the U.S. Department of Health, Education, and Welfare only after its existence was publicized and it became a political embarrassment.

The Nuremberg code paved the way for the Helsinki declaration (DoH) of 1964 formulated by the World Medical Association. DoH emphasizes the fundamental ethical principles for conducting



biomedical research and specified guidelines for research conducted either by a physician, in conjunction with medical care or within a clinical setting. Its main guidelines include but not limited to: Research with humans should be based on the results of laboratory and animal experimentation. Research protocols should be reviewed by an independent committee prior to initiation and Informed consent. Research should be conducted by medically/scientifically qualified individuals and Risks should not exceed benefits. The Helsinki declaration was revised in 1975, 1983, 1989, 1989, 2000, and 2008 and is the basis for Good Participatory Practices.

The report on the atrocities which emerged from the Tuskegee Syphilis Study led to the formation of the National Research Act of 1974. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was formed. The Commission Identified the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted by those principles. As a result, in 1979, the Belmont Report was developed. The report summarized the core principles identified by the Commission to three specific guidelines for conduct of research:

- 1 *Respect of persons: devoid of race, ethnic background, financial status, gender, etc*
- 2 *Beneficence: a study must be minimal risk*
- 3 *Justice*

"The Nuremberg, Belmont and Helsinki guidelines initiated the foundation of more ethically standard research to which stringent rules and consequences for violation were outlined." Governmental laws and regulations concerning the responsible conduct of research have since been developed for research that involves both human and animal.

1. *(Code of Federal Regulations (CFR) Title 45 (public welfare), Part 46 (protection of human subjects) developed in 1931 which outlines requirements for IRB formation, composition and roles, compliance by research institutions and protection of vulnerable groups.*
2. *The animal welfare act which governs research using animal.*
3. *Good Participatory Practices (GPP) developed by AVAC to address stakeholder engagement before implementation, during and after a study has been closed.*
4. *International Ethical Guidelines for Biomedical Research Involving Human Subject.*
5. *Council for International Organizations of Medical Sciences (CIOMS).*
6. *Ethics of research related to healthcare in developing countries developed by the Nuffield Council on Bioethics which addresses the inequalities that exist between developed and developing countries create significant risks of exploitation when externally sponsored research is carried out.*
7. *Ethical Considerations In Biomedical HIV Prevention Trials Developed In 2000 By UNAIDS/WHO To Govern HIV Clinical Trials.*

In Kenya, the Ministry of Health in 2005 de-

veloped its guidelines titled "Kenya National Guidelines for research and development of HIV/AIDS vaccines"; to act as to a framework for developing and evaluating HIV/AIDS vaccines and a blueprint for collaboration with other agencies to accelerate research and development of HIV Vaccines. The National Commission on Science, Technology and Innovation (NACOSTI) also developed its research guidelines in 2004 titled 'Guidelines for Ethical Conduct of Biomedical Research Involving Human Subjects in Kenya.'

How Principal Investigators adhere to the guidelines

Principal Investigators, Sponsors, and IRBs have the mandate to ensure the upholding human dignity and protection of study participants from harm, discrimination, undue coercive recruitment and breach of confidentiality.

During proposal development, a Principal Investigator must ensure that the study procedures and processes adhere to the three fundamental ethics guidelines i.e. beneficence, respect for persons and justice. A proposal that adheres to the 3 principles of ethics must fulfill the following requirements.

Scientific Validity

As the CIOMS guidelines state: Scientifically unsound research on human subjects is unethical in that it may expose subjects to risks or inconvenience to no purpose. A scientifically viable proposal should be one that has clear scientific and clear achievable objective and meet one of the below-listed options:

1. Provide tools that have potential to lead to breakthrough in health-related research
2. Diagnose, treat, prevent or manage disease
3. Promote healthy patient behaviors
4. Better integrate care providers, patients, and healthcare systems

Stakeholder engagement

Guided by GPP (Good Participatory Practices), researchers have a responsibility to ensure participation by members of the public and the wider society. For this, they should involve the sponsors, host government and the community in which the research will be conducted. They must strive to adhere to the state legal and legislative laws pertaining conduct of research, rights of research subjects, data dissemination, publications, etc.

Relevant stakeholders should be engaged not only in planning and execution of research projects but even after completion of the project.

IRB approval

All research proposals must be approved by an accredited IRB before implementation. The IRB has the mandate to either accept or reject a study from being undertaken especially if it deems it a high-risk study to the participants. In a case of a multi-site study being carried out in different countries, each local IRB must review the document independently for undertaking in its countries local context.

Any study involving prisoners or the mentally sick; the IRB must ensure that a prison representative reviews and sits at the meeting during its



discussion. All IRBs must be independent of any

Principal Investigator interference or coercion.

Timely Reporting

The principal investigator is also supposed to report annually on research progress; activities carried out within the year, constraints, and give an overview of expected or anticipated events for the incoming year.

According to the OHRP Policy, annual renewals must be done on or before the IRB approval expires. Failure to that all study activities must be paused until approval is received.

Any Serious Adverse Event, Expected Adverse Events and social harms are supposed to be reported to the IRB within 24 hours after occurrence. All deviations are supposed to be reported not more than ten days after the study team is aware. Any change to the initially approved proposal must be approved by the IRB before it's incorporated into the main document. Any other unanticipated events to the study must also be reported to the IRB.

Ethical Considerations

This is a section that is mandatory in all medical research proposals. This section outlines

1. Risks

This should be described in detail. The researcher should try to minimize disturbance and procedures used should be minimal risk. Measures to mitigate unforeseen risks should also be outlined.

2. Benefits

Any direct or indirect benefit to participation should be listed. Any compensation for participation, medical care or allowances should also be indicated and justified. The benefit to research and policy should also be listed.

3. Confidentiality

Participant confidentiality should be upheld,

maintained and respected. Researchers have a duty to ensure they don't infringe into the participants "private space." They should make sure that the consenting is conducted in a secluded place free of noise and interruptions. Limits to confidentiality should also be outlined in detail and mitigation efforts provided.

The researcher should also weigh the amount of information required from the participant and its input into the study. Information derived should be treated as confidential. Measures should be taken for storage to ensure security is maximized and the information is not leaked. Data should also be identified and materials destroyed once research is completed.

For studies involving animals, this section must describe methods to minimize pain and distress and the process of killing the animals after research. The method of euthanasia should be specified.

Informed Consent Document

This is a document that informs the research participant about the research study allows for his/her voluntary participation. It should be signed by the participant after he/she has been explained to on the nature, the objectives, the procedures, the samples needed, collection methods of the samples, what happens to the samples after collection, benefits and risks of participation, confidentiality and limits to confidentiality

The informed consent document must also outline that participation is voluntary and that the research participant can withdraw from the study at will. The consent document should be in the simplest language easily understandable by the research participant and if need be should be translated to the local language. An assent form is also mandatory for research involving children.

For children and the mentally incapacitated, a proxy decision maker especially a parent or guardian is given authority to make the decision for participation on their behalf.

Clinical Trials

For a clinical trials, the vaccine or drug must first have been tested on animals and its risk and toxicity value assessed before it is tested on humans. The study investigator should be a qualified clinician or medical personnel (Proof of this must be provided) A clinical trial must lead to improvements in health care or add value to scientific inventions, diagnostic and therapeutic interventions. The study should have a favorable risk-benefit ratio, and principal researcher should ensure that the procedures proposed in the study minimize risks of participation.

Training

Investigators need to ensure that their study staff are trained on research methods and procedures. They should also be well versed with the consenting process to ensure recruitment is confidential, voluntary and free of any coercion. Retraining should be conducted every often to ensure compliance to the approved methods. The study staff should also develop their SOPs to govern their conduct of research.

MORE READING

1. CIOMS Working Group on the Revision of the 2002 CIOMS Ethical Guidelines for Biomedical Research LINK:<http://www.cioms.ch/index.php/2012-06-10-08-47-53/ethics/ci-oms-guidelines-working-group>
2. Website: www.ministryofhealth.go.ke
3. <http://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-continuing-review-2010/#>
4. World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.
5. Susan Folkman, PhD, "Ethics in Research with Human Participants" (APA, 2000)
6. The Nuremberg Code from "Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10," vol. 2, Nuremberg, October 1946–April 1949. (Washington, DC: US Government Printing Office, 1949).
1. International Guidelines for Ethical Review of Epidemiological Studies (CIOMS), Geneva 1991.
2. Operational Guidelines for Ethics Committees that Review Biomedical Research. World Health Organization, Geneva 2000.
3. Research Clearance in Kenya; Procedures and Guidelines by National Council for Science and Technology. NCST No. 15, 1984.
4. International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS) in collaboration with the World Health Organization, Geneva, 1993.

HOW TO CHANGE PI IN THE RESEARCH PROTOCOL

What SERU Expects.

By Benedict Kiilu, SERU.



I. Change of PI in a research protocol

A research study requires stewardship for its implementation after approval by the relevant regulatory agencies and institutions [1]. The Chief Investigator, mainly/commonly referred to as the Principal Investigator at KEMRI, is responsible for the study's implementation and ensuring that it is compliant with both local and international research guidelines such as: Food and Drug Administration (FDA) Regulations, NACOSTI research guidelines, KEMRI Research guidelines and the current Scientific and Ethics Review Unit (SERU) Standard Operating Procedures (SOPs).

In the course of implementation of a study, there may be situations such as changes in leadership of the study prompted by resolutions of the study management due to various factors or external recommendations by partners (sponsors, monitors etc) who have jurisdiction over the study ac-

tivities.

It is mandatory for any change on the investigators to be brought to the attention of the IRB that approved the study for review. The change will be effected once the board reviews the request and approves the justification provided. This article cites and details the requirements set by the SERU (KEMRI'S mandated IRB) when such a request is submitted for review.

II. Method

The retrospective data analysis on the various requests reviewed at SERU with regard to change of PI show that the following are the common reasons for the change of PIs.

III. Reasons for change

A. Appointment

There are various reasons why appointment can lead to a Principal Investigator relinquishing their position. The following are the main two forms

noted at SERU;

1. **Administrative Appointment**

A PI might be called into a managerial position at an institutional level or a government position to serve on a certain basis. This might prompt the study team to delegate the leadership roles to an investigator listed in the study or outside the study aligned with the same expertise.

2. **Promotion of (a) Co-Investigator(s)**

An investigator in the study may be called to assume the Principal Investigator's roles following recommendations by the IRB (Institution) or the study sponsor following either need to assert the new PI's expertise or disciplinary actions after research misconduct.

3. **Expertise**

The study team might appoint a Principal Investigator with mastery of the particular research perspective the study is focusing on. The expert may be part of the study team or join the study.

B. **Death**

If the Principal Investigator passes away while the study is ongoing, the study team will have to appoint a new PI to conduct study activities.

C. **Recommendations from the Study Sponsor/Collaborators**

The study sponsors may decide to appoint a new Principal Investigator (PI) to continue with the implementation of the study. This may be informed by monitoring recommendations or IRB recommendation.

D. **Conflict of Interest**

A financial or non-financial conflict of interest may arise thus, hindering the PI in discharging their duty. This would therefore prompt the need to appoint a new PI in the study.

E. **IRB Recommendation**

After a thorough review by the IRB, a new PI may be recommended to take charge of the issue

in question to ensure compliance and objective continuity of the study.

IV. **SERU Requirements**

In the case of a change of the Principal Investigator, the following requirements [2] have to be met for the request to be accepted and reviewed:

The application will then be reviewed by the board (full board review) and decision communicated.

SERU Requirements for Change of PI

- The cover letter of the request signed by the new Principal Investigator.
- A withdrawal/resignation letter by the outgoing PI.
- An amendment (SERU) form duly filled with proper justification as to the proposed change(s) (The new PI will sign off the form).
- If the new PI wasn't part of the study team, they will need to attach their Curriculum Vitae and Ethics Certificate (valid; not beyond the recommended 3 years); and a current medical license if they are medical doctors.
- A copy of the revised proposal with the list of investigators updated.

The justification of the change of PI should however be properly articulated to ensure that the interest of the IRB, outgoing principal investigator and Sponsoring entity are protected and upheld.

REFERENCES

- [1] <http://www.mtu.edu/research/administration/sponsored-programs/office/award-information/changing-pi.html>
- [2] KEMRI/SERU Standard of Procedures _www.kemri.org

ROLES OF INVESTIGATORS.

Adapted from GUIDELINE FOR GOOD CLINICAL PRACTICE ICH Harmonised Tripartite Guideline pg 12-20

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s),

and their trial-related duties and functions.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/

institution should provide to the IRB/IEC all documents subject to review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2 The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- (a) to the IRB/IEC for review and approval/favourable opinion,
- (b) to the sponsor for agreement and, if required,
- (c) to the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should as-

sign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution..

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favourable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial,

including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects

should include explanations of the following:

- (a) That the trial involves research.
- (b) The purpose of the trial.
- (c) The trial treatment(s) and the probability for random assignment to each treatment.
- (d) The trial procedures to be followed, including all invasive procedures.
- (e) The subject's responsibilities.
- (f) Those aspects of the trial that are experimental.
- (g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- (h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- (i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- (j) The compensation and/or treatment available to the subject in the event of trial-related injury.
- (k) The anticipated prorated payment, if any, to the subject for participating in the trial.
- (l) The anticipated expenses, if any, to the subject for participating in the trial.
- (m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- (n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- (o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the

trial are published, the subject's identity will remain confidential.

- (p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
 - (q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
 - (r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
 - (s) The expected duration of the subject's participation in the trial.
 - (t) The approximate number of subjects involved in the trial.
- 4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.
- 4.8.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative

provided the following conditions are fulfilled:

- (a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.
- (b) The foreseeable risks to the subjects are low.
- (c) The negative impact on the subject's well-being is minimized and low.
- (d) The trial is not prohibited by law.
- (e) The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9 Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a

CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the

investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

Roles of Principal Investigators in Clinical Trials in Kenya

Adapted from "GUIDELINES FOR CONDUCT OF CLINICAL TRIALS IN KENYA" Revision No. 1 Effective Date 1st Sept 2016 pages 5- 7

4. Investigator

4.1. Investigators shall satisfy the following:

4.1.1. The investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial and should provide evidence of such qualifications and experience through an

up to date Curriculum Vitae.

4.1.2. The investigator should have a current practice licence from the Kenya Medical Practitioners and Dentist Board

4.1.3. The investigator should be thoroughly familiar with the characteristics and appropriate use of the investigational product as described in the protocol, current investigator's brochure, in the product information and in other information sources.

4.1.4. Have a clear understanding and willingness to obey the ethical, GCP and legal requirements in the conduct of the trial.

4.1.5. To permit monitoring and auditing of the trial and inspection by PPB or appointed representatives.

4.1.6. Keep a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.1.7. The Principal Investigator must be an appropriately qualified and competent person having practical experience within the relevant professional area, who is resident in Kenya and who is responsible for the conduct of the clinical trial at a clinical site.

4.1.8. A Principal Investigator must have had previous experience as a coinvestigator in at least two trials in the relevant professional area.

4.1.9. All investigators in a clinical trial as well as the trial monitor must have had formal training in Good Clinical Practice (GCP) within the

last two years.

4.1.10. Have adequate to carry out the study

4.2. Upon signing the application form, all parties accept the responsibility that all applicable regulations and requirements will be adhered to. Furthermore, all parties are responsible for ensuring that the trial is based on and implemented according to well – founded ethical and scientific principles, which are expressed in the Helsinki Declaration and its current revisions as well as in the local and international guidelines for GCP.

4.3. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, investigational product and their trial-related duties and functions.

Adequate Resources

4.4. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.5. The investigator should have adequate number of qualified staff and adequate facilities for the duration of the trial to conduct the trial properly and safely.

4.6. The study should have adequate fund to carry out the clinical trial to its conclusion

Medical Care of Trial Subjects

4.7. A qualified medical practitioner should be responsible for all trial-related medical decisions. The qualified medical practitioner should also be licensed with the Kenya Medical and Practitioners' Board. In addition, they must have the annual Practice License.

4.8. The medical care given to, and medical decisions made on behalf of the subjects must always be the responsibility of a qualified medical practitioner or when appropriate a

qualified dentist registered with the Kenya Medical and Practitioners' Board

4.9. During and following a subject's participation in a trial, the investigator should ensure adequate medical care is provided to a subject for any adverse events including clinically significant laboratory values related to the trial.

4.10. The subject should be informed when medical care is needed for intercurrent illness for which the investigator becomes aware.

4.11. Before initiating a trial the Principal Investigator should have the written and dated approval from the Pharmacy and Poisons Board and other relevant bodies.

4.12. The investigator should conduct the trial according to the approved protocol.

4.13. The investigator shall not implement any deviation from or changes to the protocol and Informed Consent Form without prior review and approval of the

4.14. PPB and ERC except when the changes involve only logistical or administrative aspects of the trial e.g. monitor or telephone number changes or is based on issues relating to the immediate safety of subjects already recruited into the trial.

4.15. The investigator shall establish SOPs for investigational products (IP)

4.16. A Pharmacist who shall maintain records of the delivery process and who ensures that the product is processed and stored correctly should keep the IP(s).

4.17. The Pharmacist should maintain an inventory of the IP at the site, those used by each subject and the return to sponsor or alternative disposition of unused product(s).

4.18. The investigational product(s) should be used only on the subjects participating in the trial.

4.19. The investigator should ensure that the IP are used only in accordance with the approved protocol.

4.20. The investigator should ensure that if there is blinding, it is maintained but there should be criteria or establishment for breaking of the code.

4.21. The investigator or a person designated by the investigator should explain the correct use of the IP to each subject and should check at appropriate intervals during the trial that each subject

is following the instructions. In the case where the IP is administered to the subject the proper administration should be ensured.

4.22. The investigator shall guarantee the authenticity and confidentiality of the research data, the trial subjects' details and information provided by sponsor.

4.23. The investigator shall ensure that all data is accurately collected and recorded.

4.24. The investigator shall ensure that all serious adverse events are

reported promptly to the PPB within timelines specified in this Guideline

4.25. Proper protection procedures or treatments should be administered to trial subjects with serious adverse events.

4.26. The investigator shall submit all relevant trial data to PPB in a timely manner for validation, auditing and inspection.

Good participatory practices for the informed consent process

Adapted from "Good participatory practice Guidelines for biomedical HIV prevention trials 2011" pg 46-48

A. Research teams discuss the following topics with community stakeholders during development of the informed consent materials and procedures:

1. Who needs to be consulted locally to enable research teams to invite individuals to join the trial.
2. What local cultural practices may affect individual decision-making ability, and how working within these structures can be facilitated while ensuring protection of individual autonomy to provide informed consent.
3. The general literacy level of the population to be recruited and how to assess the literacy level of prospective participants.
4. Considerations and requirements for illiterate participants, including discussion of possibilities of who may serve appropriately as a witness to the informed consent process.
5. The prevalence of different languages in the area and which languages are required for obtaining informed consent from individuals.
6. Local and legal forms of identity (name and age) verification and local practices around the use of names.
7. The legal, local, and trial sponsor definitions of a "minor" and consideration of legal and local determinations of who can serve as a minor's guardian.
8. Locally appropriate reimbursement and compensation.
9. Appropriate strategies to ensure participant rights are protected, including voluntariness of participation, ensuring undue inducement is avoided, and mitigating the influence of social desirability in influencing individual agreement to enroll.
10. Strategies to ensure comprehension of informed consent materials and critical trial-related terms and concepts, including the use of visual or audio formats, flipcharts, props, analogies, and other supportive materials and methods.
11. Techniques to assess comprehension of trial participation and the frequency with which they are to be used.
12. Explanation of potential trial-related harms and how such harms will be addressed (see Section 3.13).
13. Strategies to ensure that follow-up of participants after missed visits respects agreements between the participant and research team about how to contact the participant.
14. Consideration of the length of informed consent forms and the estimated time required to complete the informed consent process.
15. Preferred ways for participants to contact research teams and stakeholders independent from the research team to ask questions or express concerns about trial participation.
16. Ways to pilot informed consent materials.

B Research teams maintain clear written records of discussions and agreements. This includes community stakeholder recommendations, actions taken by the research team, and any unresolved issues that require follow-up.

C Trial sponsors ensure sufficient funding and research teams create a budget and allocate funds and staff time to allow informed consent materials to be properly developed, piloted, translated, and implemented, including materials to assess participants' ongoing consent.