



REPUBLIC OF KENYA

Guidelines for Ethical Conduct of Biomedical Research Involving Human Subjects in Kenya

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Foreword

Kenya has a fairly elaborate research system comprising of regulatory and executing institutions. The research system comprises the National Council for Science and Technology (NCST); the Ministry of Education, Science and Technology; public research institutes; commodity-based research institutes, institutions of higher learning; and semi-private non-governmental organizations. However, health research in Kenya is carried out in various institutions, both public and private.

The National Council for Science and Technology (NCST) and the Ministry of Education, Science and Technology through the Department of Research Development are the institutions overseeing research in the country. The legal framework of science and technology is provided by the Science and Technology Act of 1979. Any research planned to be undertaken in the country requires clearance and authorization.

“The research clearance procedures and guidelines in Kenya,” 1984 edition, is about clearance of all research conducted in the country. There is therefore need for specific research and ethical guidelines involving human subjects.

In this document we have attempted to draft ethical guidelines using internationally recognized reference material. We think that these guidelines will go a long way in sealing the loopholes that have existed in the current medical research regulatory mechanism in Kenya.

We have also given direction as to how to constitute an ethical committee in terms of membership requirement, appointments, offices, quorum requirements and education for Ethical Committee members.

This document we hope will not be static but will continue to evolve as new ethical challenges emerge in the future medical research involving human subjects.

Background to Evolution of Medical Research Ethics

Before 1947, there are no available records to show that there existed any form of medical research ethics except the medical practice ethics. However, in 1947, the Nuremberg Code was written. The code derives its name from a town in Germany where the code was conceived and formulated. The code came into existence as a response to the atrocities the German physicians had visited on the Jews, Russians and tubercular Poles with the help of their government during the Second World War. These people, who were prisoners of war, were subjected to extremely inhuman experimentations that resulted in the death of many of them; and those who survived were left with severe scarring and other deformities. The objective of the Nuremberg Code was to ensure that such atrocities were not repeated anywhere in the world. The code underscored the importance of voluntary consent of the human subject before being made to participate in any medical research. It also underscored the importance of doing experimentation in animals before using human subjects in biomedical research. In the United States of America the scandal such as Tuskegee and Willowbrook gave rise to the development of the Belmont Report, which was meant to provide broad principles that could be used to generate specific rules and regulations in the conduct of biomedical research involving human subjects. It specifically focused on the use of informed consent, favourable risk-benefit ratio, and the need to ensure that vulnerable populations are not targeted for risky research. Because the Advisory Committee on Human Radiation Experiments in the USA was responding to covert radiation experiments, it underscored the importance of honesty in such experiments among its six ethical standards and rules. Most other major documents do not highlight this.

In 1964, the World Medical Association developed the Declaration of Helsinki document. Its purpose was to provide guidance to physicians and other participants in medical research on ethical principles to be adhered to as they conduct biomedical research involving human subjects. Since then the document has undergone multiple revisions in Tokyo, Japan, in 1975; Venice, Italy, in 1983; Hong Kong in 1989; Somerset West, South Africa, in 1996; and lastly Edinburgh, Scotland, in 2000. In 1982, the World Health Organization (WHO) and the Council for International Organizations of Medical Sciences (CIOMS) published “Proposed International Guidelines for Biomedical Research Involving Human Subjects”. The purpose of this document was to give guidance on how the Helsinki Declaration ethical principles could be effectively applied in developing countries, taking into consideration the culture, socio-economic conditions, national laws and executive administrative arrangements.

These proposed guidelines were reviewed so as to take into account ethical issues that had arisen from the advent of HIV/AIDS pandemic, such as drug and vaccine trials in human subjects. After this review, the 1982 proposed guidelines were superseded by publication in 1993 of “International Ethical Guidelines for Biomedical Research Involving Human Subjects.” This document was adopted at a Health Research Ethics in Africa seminar in Arusha, Tanzania, on 15 January 2001 as the minimum requirement for ethical biomedical research involving human subjects in Africa. However, this document has not yet received widespread utility in most African countries. To date, there are some African countries that conduct biomedical research involving human subjects with either inadequately constituted ethical committees or in some cases with no ethical committees at all.

In Kenya, the legal framework for science and technology came into existence in 1979 under the Science and Technology Act. The act established the National Council of

Science and Technology and all the public research institutes. The National Council for Science and Technology has been empowered to coordinate all research in Kenya and advise the government on all matters related to research. This function entails the documentation, knowledge of all research in the country and all the institutions in which the research is being conducted. For research of a biomedical nature to be conducted on humans in Kenya, ethical clearance is mandatory. Institutional ethical clearance committees do the ethics clearance. The Kenya Medical Research Institute, Kenyatta National Hospital, Eldoret Referral Hospital and Aga Khan Hospital have ethics clearance committees. However, only the Kenya Medical Research Institute has research guidelines. Most researchers who do not belong to these institutions but wish to do clinical research are often advised to be affiliated to any one of the institutions and have their proposals reviewed by the appropriate ethics committees. However, since biomedical research involving human subjects is rapidly expanding in the country with the involvement of an increasing number of non-governmental institutions, as a result of the HIV/AIDS pandemic, the National Council for Science and Technology must position itself strategically in order to be able to efficiently and effectively coordinate all research in this area. One of the ways to do that is to set standards to be complied with by those who wish to conduct research involving human experimentation. These standards must necessarily be scientific and ethical in nature and universally acceptable.

The current clearance and control mechanism is weak with many loopholes, which have been exploited in the past in this country by people who do not want to do sound scientific and ethically acceptable research. In such circumstances, the council should have powers to audit such works and mete out appropriate sanctions on such individuals if found to be peddling falsehood. It is hoped that the development of ethical guidelines by the Council for Sound Conduct of biomedical research involving human subjects with HIV/AIDS will go along way in assisting it to regulate research efficiently and effectively. Before going into the specifics of the relevant ethics of biomedical research, it is appropriate at this point to provide a systematic and coherent framework for determining whether a study is ethical.

A Systematic and Coherent Framework for Determining Whether Clinical Research Is Ethical

The overarching objective of clinical research is to develop generalizable knowledge to improve health and/or increase understanding of human biology; subjects who participate are the means of securing such knowledge. By placing some people at risk of harm for good of others, clinical research has the potential for exploitation of human subjects. Ethical requirements for clinical research aim to minimize the possibility of exploitation by ensuring that research subjects are not merely used but are treated with respect while they contribute to the social good. There are seven requirements that provide for this framework.

These requirements are listed in chronological order from the conception of the research to its formulation and implementation. They are meant to guide the ethical development, implementation, and review of individual clinical protocols. These seven requirements are discussed in detail below.

1) *Value*

To be ethical, clinical research must be valuable, meaning that it evaluates a diagnostic or therapeutic intervention that could lead to improvements in health or well-being; or a

preliminary etiological, pathophysiological, or epidemiological study to develop such an intervention; or tests a hypothesis that can generate important knowledge about structure or function of human biological systems, even if that knowledge does not have immediate practical ramifications. Examples of research that would not be socially or scientifically valuable include clinical research with non-generalizable results, or substantial or total overlap with proven results. In addition, research with results unlikely to be disseminated or in which the intervention could never be practically implemented even if effective is not valuable. Only if society will gain knowledge, which requires sharing results, whether positive or negative, can exposing human subjects to risk in clinical research be justified. Thus evaluation of clinical research should ensure that the results will be disseminated, although publication in peer-reviewed journals need not be the primary or only mechanism.

There are two fundamental reasons why social, scientific, or clinical value should be an ethical requirement: responsible use of finite resources and avoidance of exploitation. Research resources are limited. Even if major funding agencies could fund all applications for clinical research, doing so would divert resources from other worthy social pursuits. Beyond not wasting resources, researchers should not expose human beings to potential harm without some possible social or scientific benefit.

It is possible to compare the relative value of different clinical research studies; clinical research that is likely to generate greater improvements in health or well-being given the condition being investigated, the state of scientific understanding, and feasibility of implementing the intervention is of higher value. Comparing relative value is integral to determination of funding priorities when allocating limited funds among alternative research proposals. Similarly, a comparative evaluation of value may be necessary in considering studies involving finite scientific resources such as limited biological material or the small pool of long-term human immunodeficiency virus non-progressors.

2) *Scientific Validity*

To be ethical, valuable research must be conducted in a methodologically rigorous manner. Even research asking socially valuable questions can be designed or conducted poorly and produce scientifically unreliable or invalid results. As the CIOMS guidelines succinctly state: Scientifically unsound research on human subjects is unethical in that it may expose subjects to risks or inconvenience to no purpose.

For a clinical research protocol to be ethical, the methods must be valid and practically feasible: the research must have a clear scientific objective; be designed using accepted principles, methods, and reliable practices; have sufficient power to definitively test the objective; and offer a plausible data analysis plan. In addition, it must be possible to execute the proposed study. Research that uses biased samples, questions, or statistical evaluations, that is underpowered, that neglects critical end points, or that could not possibly enrol sufficient subjects cannot generate valid scientific knowledge and is thus unethical. For example, research with too few subjects is not valid because it might be combined in a meaningful meta-analysis with other, as yet unplanned and unperformed clinical research; the ethics of a clinical research study cannot depend on the research that others might but have not yet done. Of course the development and approval of a valid method is of little use if the research is conducted in a sloppy or inaccurate manner; careless research that produces uninterpretable data is not just a waste of time and resources, it is unethical.

Clinical research that compares therapies must have “an honest null hypothesis”. That is, there must be controversy within the scientific community about whether the new intervention is better than standard therapy, including placebo, either because most clinicians and researchers are uncertain about whether the new treatment is better, or because some believe the therapy is better while others believe the investigational intervention superior. If there exists a consensus about what is the better treatment, there is no null hypothesis, and the research is invalid. In addition, without clinical equipoise, research that compares therapies is unlikely to be of value because the research will not contribute to increasing knowledge about the best therapy, and the risk-benefit ratio is unlikely to be favourable because some of the subjects will receive inferior treatment.

Importantly, a “good question” can be approached by good or bad research techniques; bad research methods do not render the question valueless. Thus, the significance of a hypothesis can and should be assessed prior to and independent of the specific research methods. Reviewers should not dismiss a proposal that uses inadequate methods without first considering whether adjustments could make the proposal scientifically valid.

The justification of validity as an ethical requirement relies on the same two principles that apply to value—limited resources and the avoidance of exploitation. Invalid research is unethical because it is a waste of resources as well: of the investigator, the funding agency, and anyone who attends to the research. Without validity the research cannot generate the intended knowledge, cannot produce any benefit, and cannot justify exposing subjects to burdens or risks.

3) *Fair Subject Selection*

The selection of subjects must be fair. Subject selection encompasses decisions about who will be included both through the development of specific inclusion and exclusion criteria and strategy adopted for recruiting subjects, such as which communities, which study sites and which potential groups will be approached. There are several facets to this requirement.

First, fair subject selection requires that the scientific goals of the study, not vulnerability, privilege, or other factors unrelated to the purpose of the research, be the primary basis for determining the groups and individuals that will be recruited and enrolled. In the past, groups sometimes were enrolled, especially for research that entailed risks or offered no potential benefits, because they were “convenient” or compromised in their ability to protect themselves, even though people from less vulnerable groups could have met the scientific requirements of the study.

Similarly, groups or individuals should not be excluded from the opportunity to participate in research without a good scientific reason or susceptibility to risk that justifies their exclusion. It is important that the results of research be generalizable to the populations that will use the intervention. Efficiency cannot override fairness in recruiting subjects. Fairness requires that women be included in the research, unless there is good reason, such as excessive risk, to exclude them. This does not mean that every woman must be offered the opportunity to participate in research, but it does mean that women as a class cannot be preemptorily excluded.

Second, it is important to recognize that subject selection can affect the risks and benefits of the study. Consistent with the scientific goals, subjects should be selected to minimize risks and enhance benefits to individual subjects and society. Subjects who are eligible based on the scientific objectives of a study but are at substantially higher risk of being

harmed or experiencing more severe harm should be excluded from participation. Selecting subjects to enhance benefits entails consideration of which subjects will maximize the benefit or value of the information obtained. If a potential drug or procedure is likely to be prescribed for women or children if proven safe and effective, then these groups should be included in the study to learn how the drug affects them. Indeed, part of the rationale for recent initiatives to include more women, minorities, and children in clinical research is to maximize the benefits and value of the study by ensuring that these groups are enrolled. It is not necessary to include children in all phases of research. Instead, it may be appropriate to include them only after the safety of the drug has been assessed in adults.

Additionally, fair subject selection requires that, as far as possible, groups and individuals who bear the risks and burden of research should be in a position to enjoy its benefits, and those who may benefit should share some of the risks and burdens. Groups recruited to participate in clinical research that involves a condition to which they are susceptible or from which they suffer are usually in a position to benefit if the research provides a positive result, such as a new treatment. For instance, selection of an antimalarial vaccine should consider not only who will best answer the scientific question, but also whether the selected groups will receive the benefits of the vaccine, if proven effective. Groups of subjects who will predictably be excluded as beneficiaries of research results that are relevant to them typically should not assume the burden so that others can benefit. However, this does not preclude the inclusion of subjects who are scientifically important for a study but for whom the potential products of the research may not be relevant, such as health control subjects.

Fair subject selection should be guided by the scientific aims of the research and is justified by the principles that equals should be treated similarly and that both the benefits and burdens generated by social cooperation and activities such as clinical research should be distributed fairly. This does not mean that individual subjects and members of groups from which they are selected must directly benefit from each clinical research project or that people who are marginalized, stigmatized, powerless, or poor should never be included. Instead, the essence of fairness in research on human subjects is that scientific goals, considered in dynamic interaction with the potential for distribution of risks and benefits, should guide the selection of subjects.

4) *Favorable Risk–Benefit Ratio*

Clinical research involves drugs, devices and procedures about which there is limited knowledge. As a result, research inherently entails uncertainty about the degree of risk and benefits with earlier phase research having greater uncertainty. Clinical research can be justified only if, consistent with the scientific aims of the study and relevant standards of clinical practice, three conditions are fulfilled: the potential risks to individual subjects are minimized, the potential benefits to individual subjects are enhanced, and the potential benefits to individual subjects and society are proportionate to or outweigh the risks.

Assessment of the potential risks and benefits of clinical research by researchers and review bodies typically involves multiple steps. First, risks are identified and, within the context of good clinical practice, minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

Second, potential benefits to individual subjects from the research are delineated and enhanced. Potential benefits focus on the benefits to individual subjects, such as health improvement, because the benefits to society through the generation of knowledge are assumed if the research is deemed to be of a value and valid. The specification and enhancement of potential benefits to individual subjects should consider only health-related potential benefits derived from the research. Assessment of the research plan should determine if changes could enhance the potential benefits for individual subjects. For example, consistent with the scientific objectives, tests and interventions should be arranged to increase benefit to subjects. However, extraneous benefits, such as payment, or adjunctive medical services, such as the possibility of receiving a hepatitis vaccine not related to the research, cannot be considered in delineating the benefits compared with the risks, otherwise simply increasing payment or adding more unrelated services could make the benefits outweigh even the riskiest research. Furthermore, while participants in clinical research may receive some health services and benefits the purpose of clinical research is not the provision of health services. Services directly related to clinical research are necessary to ensure scientific validity and to protect the well-being of the individual subjects.

In the final step, risks and potential benefits of the clinical research interventions to individual subjects are compared. In general, the more likely and/or severe the potential risks the greater is likelihood and/or magnitude of the prospective benefits must be; conversely, research entailing potential risks that are less likely and/or of lower severity can have more uncertain and/or circumscribed potential benefits. If the potential benefits to subjects are proportional to the risks they face, as generally found when evaluating phase 2 and 3 research, then the additional social benefits of the research, assured by the fulfilment of the value and validity requirements, imply that the cumulative benefits of the research outweigh its risks.

Obviously, the notions of “proportionality” and potential benefits “outweighing” risks are non-quantifiable. However, the absence of a formula to determine when the balance of risks and potential benefits is proportionate does not connote that such judgements are inherently haphazard or subjective. Instead, assessments of risks and potential benefits to the same individuals can appeal to explicit standards, informed by existing data on the potential types of harms and benefits, their likelihood of occurring, and their long-term consequences. People routinely make justifiable intrapersonal comparisons of risks and benefits for themselves and even for others, such as children, friends and employees, without the aid of mathematical formulae.

An additional evaluation is necessary for any clinical research that presents no potential benefits to individual subjects, such as phase I safety, pharmacokinetic, and even some epidemiology research, or when the risks outweigh the potential benefits to individual subjects. Determination of when potential social benefits outweigh risks to individual subjects requires interpersonal comparisons that are conceptually and practically more difficult. However, policymakers often are required to make these kinds of comparisons, for example when considering whether pollution and its attendant harm to some people are worth the potential benefits of higher employment and tax revenues to others. There is no settled framework for how potential social benefits should be balanced against individual risks. Indeed, the appeal to a utilitarian approach of maximization, as in cost-benefit analysis, is quite controversial both morally and because many risks and benefits of research are not readily quantifiable on commensurable scales. Nevertheless, these comparisons are made, and regulations mandate that investigators and institutional

review boards (IRBs) make them with respect to clinical research. When research risks exceed potential medical benefits to individuals and the benefit of useful knowledge to society, the clinical research is not justifiable.

The requirement for a favourable risk benefit ratio embodies the principles of non-malefeasance and beneficence, long recognized as fundamental values of clinical research. The principle of non-malefeasance states that one ought not to inflict harm on a person. This justifies the need to reasonably reduce the risks associated with research. The principle of beneficence “refers to a moral obligation to act for the benefit of others”. In clinical research, this translates into the need to enhance the potential benefits of the research for both individual subjects and society. Ensuring that the benefits outweigh the risks is required by the need to avoid the exploitation of subjects.

5) *Independent Review*

Investigators inherently have multiple, legitimate interests—interests to conduct high-quality research, complete the research expeditiously, protect research subjects, obtain funding, and advance their careers. These diverse interests can generate conflicts that may unwittingly distort the judgement of even well-intentioned investigators regarding the design, conduct and analysis of research. Wanting to complete a study quickly may lead to the use of questionable scientific methods or readily available rather than the most appropriate subjects. Independent review by individuals unaffiliated with the clinical research helps minimize the potential impact of such conflicts of interest. For some research with few or no risks, independent review may be expedited, but for much of clinical research, review should be done by a full committee of individuals with a range of expertise who have the authority to approve, amend or terminate a study.

Independent review of clinical research is also important for social accountability. Clinical research imposes risks on subjects for the benefit of the society. Independent review of a study’s compliance with ethical requirements assures members of society that people who enrol in trials will be treated ethically and that some segments of society will not benefit from the misuse of other human beings. Review also assures people that if they enrol in clinical research, the trial is ethically designed and the risk-benefit ratio is favourable.

In the United States, independent evaluation of research projects occurs through multiple groups including granting agencies, local IRBs, and data and safety monitoring boards. In other countries independent review of clinical research is conducted in other ways. In Kenya evaluation of scientific research is done through scientific and ethical review committees in the relevant local institutions charged with the responsibility of conducting research in human subjects.

6) *Informed Consent*

Of all requirements, none has received as much emphasis as informed consent. The purpose of informed consent is twofold: to ensure that individuals control whether or not they enrol in clinical research and participate only when the research is consistent with their values, interests and preferences. To provide informed consent, individuals must be accurately informed of the purpose, methods, risks, benefits and alternatives to the research; understand this information and its bearing on their own clinical situation; and make a voluntary and uncoerced decision whether to participate. Each of these elements is necessary to ensure that individuals make rational and free determinations of whether the research trial is consonant with their interests.

Informed consent embodies the need to respect persons and their autonomous decisions. To enrol individuals in clinical research without their authorization is to treat them merely as a means to purposes and ends they may not endorse and deny them the opportunity to choose what projects they will pursue.

Children and adults with diminished mental capacity who are unable to make their own decisions about participating in research nonetheless have interests and values. For instance, individuals rendered unconscious due to head trauma or a stroke typically retain the interests and values they had just before the accident. Even individuals with severe Alzheimer disease retain some interests, if only those related to personal dignity and physical comfort. Showing respect for these non-autonomous persons means ensuring that research participation is consistent with their interests and values; this usually entails empowering a proxy decision maker to determine whether to enrol the person in clinical research. In making this decision, the proxy uses the substituted judgement standard: what research decision would the subject make if he or she could.

However, an individual's preferences and values related to clinical research may be unknown or unknowable or, in the case of children the individual may not have developed mature preferences related to research. In such cases, research proxies should choose the option that is in the individual's best medical interests. There is controversy about how much discretion proxies should have in such circumstances, especially given the inherent uncertainty of the risks and potential benefits of research participation. The National Bioethics Advisory Commission has urged that proxies should exercise "great caution" in making judgements about a subject's best interest regarding research. Other groups believe that proxies should have more discretion.

In emergency settings that preclude time for identifying and eliciting the consent of a proxy decision maker research can proceed without either informed consent or permission of proxy decision makers when conducted under strict guidelines. Most importantly, there should be clinical equipoise—the absence of consensus regarding the comparative merits of the interventions to be tested. In such a case, the subject is not worse off by enrolling.

7) *Respect for Potential and Enrolled Subjects*

Ethical requirements for clinical research do not end when individuals either sign the consent form and are enrolled or refuse enrolment. Individuals must continue to be treated with respect from the time they are approached—even if they refuse enrolment—throughout their participation and even after their participation ends. Respecting potential and enrolled subjects entails at least five different activities. First, since substantial information will be collected about potential as well as enrolled subjects, their privacy must be respected by managing the information in accordance with confidentiality rules. Second, respect includes permitting subjects to change their mind, to decide that the research does not match with their interests, and to withdraw without penalty. Third, in the course of clinical research new information about the effect of the intervention or the subject's clinical condition may be gained. Respect requires that enrolled subjects be provided with this new information. For instance, when informed consent documents are modified to include additional risks or benefits discovered in the course of research, subjects already enrolled should be informed. Fourth, the welfare of subjects should be carefully monitored throughout their research participation. If subjects experience adverse reactions, untoward events, or changes in clinical status, they should be provided with appropriate treatment and, when necessary, removed from the study. Finally, to

recognize subjects' contribution to clinical research, there should be some mechanism to inform them of what was learned from the research.

For commentators used to thinking about respect in terms of privacy and confidentiality alone, these different activities may seem a haphazard agglomeration of informed consent, confidentiality and other protections. In fact, this requirement integrates into a coherent framework, actions the commonality of which often goes unrecognized. It reminds investigators, subjects, IRB members and others that respect for subjects requires the respectful treatment of individuals who choose not to enrol and the careful ongoing monitoring of those who do, in addition to ensuring the privacy and confidentiality of enrolled subjects. This requirement emphasizes that the ethics of clinical research do not end with the signing of a consent document but encompass the actual implementation, analysis and dissemination of research. Indeed, it suggests that although "human subjects" is the prevailing designation, the term subject may not fully reflect appropriate respect: human research participant or partner may be more appropriate terminology.

Respect for potential and enrolled subjects is justified by multiple principles including beneficence, non-maleficence, and respect for persons. Permitting subjects to withdraw and providing them additional information learned from the research are key aspects of respecting subject autonomy. Protecting confidentiality and monitoring well-being are motivated by respect for persons, beneficence, and non-maleficence.

General Ethical Principles

All research involving human subjects must be conducted in accordance with three basic ethical principles:

1. **Respect for persons:** This involves at least two ethical considerations.
 - (a) Respect of autonomy, which requires that those capable of deliberating about their personal choices, should be treated with respect for being able to do so.
 - (b) Those with diminished autonomy or vulnerable groups should be protected against harm or abuse.
2. **Beneficence:** This refers to the ethical obligation to maximize benefits and minimize harm or wrongs.
3. **Justice:** Treatment of people in accordance with what is morally right and proper. Let people have what is due to them. In a research situation, this means equitable distribution of the benefits and the burdens of the research.

Preamble to the Guidelines

In general, research is defined as any creative systematic activity undertaken to increase the stock of scientific and technical knowledge and to devise new applications. In the case of biomedical research this means generation of knowledge that could lead to new preventive, prophylactic, therapeutic and diagnostic tools or improvements in current tools for the enhancement of health or well-being of all people.

Research investigations often begin with the construction of hypotheses and these are then tested in laboratories and in experimental animals using well-designed and rigorous scientific methodologies under the direction of highly qualified personnel. For the findings to be clinically useful experiments must also be conducted in human subject to test for the scientific validity of the information.

Although the experiments in humans are also often well and carefully designed, they still present some risks to the subjects involved in the research. However, the risk taken is justified since the individuals taking part in research may gain direct benefits and furthermore, the information gained may increase human knowledge in the relief of suffering and/or prolongation of life for the larger communities. During the conduct of research involving humans, the tendency for researchers to *use* the vulnerable or people with diminished autonomy cannot be ruled out. These guidelines are being developed as a means of protecting those human subjects taking part in research against such abuses in Kenya.

Guidelines

- 1) Biomedical research involving human subjects must conform to generally accepted scientific principles and must be based on laboratory and animal experimentation and a thorough knowledge of the scientific literature in the area of the research.
- 2) The design and performance of each experimental procedure involving human subject must be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to the ethics clearance committee, which is independent of the investigator and the sponsor of the research. For public institutions with standing ethical clearance, standing ethical committees are to be found in their institutions.

Private institutions, e.g., NGOs, individuals and groups of individuals who wish to engage in biomedical research involving humans, should affiliate themselves to public institutions mandated to do medical research in Kenya—Kenya Medical Research Institute (KEMRI), Kenyatta National Hospital, Eldoret Referral Hospital, or they can send their research proposals to the National Council for Science and Technology for evaluation and advice as to with which institution they should affiliate.

- 3) All biomedical research involving human subjects conducted in Kenya should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subjects will rest with the medically qualified person and never on the subject of the research despite the subject having given his/her consent.
- 4) Every biomedical research involving human subjects must be preceded by a careful assessment of predictable risks in comparison with the anticipated benefits to the subjects or others. The protection of the subject or subjects must always prevail over the interests of science and society.
- 5) The investigator or the investigating team should terminate any research involving humans if in his/her or their judgement it may if continued be harmful to the individual or individuals involved in the research.
- 6) For all biomedical research involving human subjects, the investigator must obtain the informed consent of the prospective subject, or in the case of an individual who is not capable of giving informed consent, the proxy consent of a properly authorized

representative. Informed consent is deemed voluntary if the individual is given the necessary information, he/she has understood the information, and after considering the information, has arrived to a decision to participate, without coercion, undue influence, intimidation or inducement.

Children, many adults with severe mental disorders or behaviour disorders, and many adults unfamiliar with modern medical concepts are limited in their capacity to give informed consent. Consent given by such individuals should not be taken as valid without prior approval by the ethics clearance committees of the relevant institution. However, in such circumstances the investigator had better get a proxy consent from a legal guardian or an authorized representative.

If the research design involves no more than minimal risk—the risk not greater than that attached to routine medical or psychological examination—and it is not practicable to obtain informed consent, for example where the research involves extracting data from the patient’s records, the ethical review of the relevant institution may waive some or all of the elements of the informed consent.

In most rural communities in Kenya due to sociocultural arrangements, women, particularly married ones, may not give their consent to participate in research without the express permission of their husbands. In such circumstances, while the husband may give his “consent”, the woman should still be allowed to give her individual consent. If after the husband has given his consent but she decides not to participate in the research, her decision not to do so must be respected. Kenya has as many as 42 tribes, and there are bound to be unique sociocultural backgrounds for each tribe. Whatever the differences and the processes for giving informed consent, the researcher must always follow the principles of getting informed consents as laid down in these guidelines.

7) Essential information for prospective research subjects.

A prospective research subject must be provided with the following information in a language he/she understands before being asked to give consent to participate in the proposed research:

- That the individual should know that he/she is being invited to participate in a research project and not a routine medical service.
- The expected duration of the subject’s participation in the research.
- The benefits that might reasonably be expected to accrue to the subject or to others as an outcome of the research. Treatment of the research subjects for other minor ailments is not a benefit accruing from the research.
- Any foreseeable risks or discomfort to the subject associated with participation in the research.
- Any alternative procedures or courses of treatment that might be as advantageous to the subject as the procedure or treatment being tested.
- The extent to which confidentiality or the records in which the subject is identified will be maintained.

- The extent of the investigator's responsibility, if any, to provide medical services to the subject.
- That therapy will be provided free of charge for specified types of research-related injury.
- Whether the subject or the subject's family or dependants will be compensated for disability or death resulting from such injury.
- That the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would be otherwise entitled.
- The individuals should be given the freedom to ask questions regarding the project.

8) Inducement to participate in a research project.

All attempts must be made to avoid unduly inducing people to participate in a research project against their better judgement. Acts of undue inducement would be, for example, giving out large sums of money, extensive medical services, blankets and other items that would induce people to consent to participate in the research. Such activities are likely to unduly influence most of the economically vulnerable groups in the community. However, small payments such as reimbursement of transport costs, limited medical services to take care of minor ailments can be given out, but the ethical clearance committee must give approval.

9) Research involving children.

Before conducting research in children, the investigator must ensure that:

- Children will not be involved in research that might equally be carried out in adults.
- The purpose of the research is to generate knowledge relevant to the health needs of children.
- A parent or legal guardian must give proxy consent. However, in a situation where the parents or the legal guardian gives proxy consent, but the child refuses to participate in the research, that refusal must be respected unless there's no other medical alternative from which the child could benefit.
- The risk presented by interventions not intended to benefit the child is low and commensurate with the importance of the knowledge to be gained.
- Interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child as any available alternative.

10) Research involving persons with mental or behavioural disorders.

An investigator must ensure that before undertaking research in individuals with mental behavioural disorders and who are incapable of giving adequately informed consent that the following conditions below are fulfilled:

- Such persons will not be subjects of research that might equally be carried out on persons in full possession of their mental faculties.

- The knowledge gained would be relevant to the particular health needs of persons with mental or behavioural disorders.
- The consent of the subject has been obtained to the extent of that subject's capabilities and a prospective subject's refusal to participate in non-clinical research is always respected.
- In the case of incompetent individuals, informed consent is obtained from a legal guardian or other duly authorized person.
- The degree of risk attached to the intervention not intended to benefit the individual subject is low and commensurate with the importance of knowledge to be gained.
- Interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual subject as any alternative.

11) Research involving prisoners.

There are opposing and persuasive arguments for and against doing research in prisons. Although no international declarations bar prisoners from participating in research, the opposing arguments preclude an internationally agreed recommendation. In many developing countries including Kenya, prison conditions are very harsh, i.e., low quality or inadequate diet, poor linen and accommodation. The prisoners are always under fear of reprisals from the prison wardens if they do not comply with any instructions given to them. However, prisoners with serious illness or at risk of serious illness, e.g., HIV/AIDS, hepatitis, cancer and TB should not be denied access to investigational drugs, vaccines or other agents that show promise of therapeutic or preventive benefit. In a situation where an investigator wishes to conduct biomedical research in Kenya on prisoners, given the above conditions in Kenyan prisons, he must ensure that the prisoners actually give consent in conditions where there is no fear of reprisals from wardens if one chooses not to participate in the particular study. The ethical committee giving clearance must ensure that there will be independent monitoring of the research projects to assure the protection of rights and the dignity of the prisoners involved in the research.

12) Research involving underdeveloped communities in both developed and developing countries.

The investigator must ensure that:

- Persons in underdeveloped communities be ordinarily involved in research that could be carried out reasonably well in developed communities. For example, it would not be ethical for an investigator to conduct research into cardiovascular diseases in slum dwellers rather than in the well-to-do members of communities from up-market estates.
- The research should be responsive to the health needs and priorities of the community in which it is to be carried out.
- Undue inducement to participate in the research is avoided at all costs.

13) Selection of pregnant or nursing (breastfeeding) women as research subjects.

Pregnant or nursing women should in no circumstances be the subjects of clinical research unless the research carries no more than minimal risk to the foetuses or nursing infants and the object of the research is to obtain new knowledge about pregnancy or lactation. As a general rule pregnant or nursing women should not be subjects of clinical trials except where such trials are designed to protect or advance the health of the pregnant or nursing women, or foetuses or nursing infants and for which women who are not pregnant or nursing would not be suitable subjects. Examples for such trials would be a trial designed to test the safety and efficacy of a drug for reducing perinatal transmission of HIV from mother to child, a trial of advice for detecting foetal abnormalities or trials of therapies for conditions associated with or aggravated by pregnancy, e.g., nausea, vomiting, hypertension or diabetes mellitus. The justification for such trials should be that they should not be arbitrarily deprived of the opportunity to benefit from investigational drugs, vaccines or other agents that promise therapeutic or preventive benefits.

14) Compensation of research subjects for accident injury or death.

Research subjects who suffer physical injury as a result of their participation in the research project have a right to compensation. They will be entitled to such financial or other assistance as would compensate them equitably for any temporary or permanent impairment or disability. In the case of death, their dependants are entitled to material compensation. The right to compensation may not be waived.

15) Informed consent for epidemiological studies.

For several epidemiological researches, it is either impracticable or inadvisable to obtain individual consent. In such circumstances the relevant ethical review committee should determine whether it is ethically acceptable to proceed without the individual informed consent and whether the investigator has put in place mechanisms to protect the safety and to respect the privacy of the research subjects, and to maintain the confidentiality of the data. Such studies would be for example, examination of medical records, or anonymous “left-over” samples of blood, urine, saliva, tissue specimens.

However, when the focus of the study is an entire community rather than individual human subject then the investigators should secure the agreement and cooperation of provincial administration through the local assistant chief or the chief. If the Divisional Officer’s (DO), the District Commissioner’s (DC) offices are within reach, the investigators may pay them courtesy calls for continued good will. The Provincial Medical Officer of Health (PMO) and the Medical Officer of the nearest health facility should be contacted and be informed of the intended study. In some areas in the country, the permission of the community leaders may be sought where this is necessary. In addition to the above requirement, if the studies involve personal contact between the investigators and the individual subjects, the general requirements of informed consent must apply.

If an individual chooses not to participate in the study despite the agreement and cooperation given to the investigators by both the official leadership through provincial administration, the local informal leadership, and the public health leadership, that decision must be respected and there should be no penalties. There is no informed consent requirement for the information already in the public domain.

The Phases of Clinical Drug Trials and Vaccines

All drug developments including antiretrovirals and vaccine development including HIV/AIDS vaccine must follow the developmental processes shown below under each subheading.

Vaccine Development

Phase I refers to the first introduction of a candidate vaccine into a human population for initial determination of its safety and biological effects, including immunogenicity. This phase may include studies of dose and route of administration and usually involves fewer than 100 volunteers. Children are never suitable candidates during this phase of vaccine development.

Phase II refers to the initial trials examining effectiveness in a limited number of volunteers (usually between 200 and 500); the focus of this phase is immunogenicity. Children are not suitable research subjects. However, a phase II vaccine trial seeking evidence of immunogenicity in infants may be justified in the case of a vaccine that has shown evidence of preventing or slowing progression from asymptomatic HIV infection to disease in adults.

Phase III trials are intended for a more complete assessment of safety and effectiveness in the prevention of disease, involving a larger number of volunteers in a multicentre adequately controlled study.

Drug Development

Phase I refers to the first introduction of a drug into humans. Normal volunteer subjects are usually studied to determine levels of drugs at which toxicity is observed. Such studies are followed by dose-ranging studies in patients for safety and, in some cases, early evidence of effectiveness. Children are not involved at this stage of development.

Phase II investigation consists of controlled clinical trials designed to demonstrate effectiveness and relative safety. Normally, these are performed on a limited number of closely monitored patients. Children may be involved if there is evidence from adult subjects that the drug has therapeutic benefit to them.

Phase III trials are performed after a reasonable probability of effectiveness of a drug has been established and are intended to gather additional evidence of effectiveness for specific indications and more precise definition of drug-related adverse effects. This phase includes both controlled and uncontrolled studies.

Phase IV trials are conducted after the national drug registration authority has approved a drug for distribution or marketing. These trials may include research designed to explore a specific pharmacological effect, to establish the incidence of adverse reactions, or to determine the effects of long-term administration of a drug. Phase IV trials may also be designed to evaluate a drug in a population not studied adequately in the pre-marketing

phases (such as children or the elderly) or to establish a new clinical indication for a drug.

Externally Sponsored Research

Externally sponsored research entails two ethical obligations.

- An external sponsoring agency should submit the research protocol to ethical and scientific review according to the standards of the country of the sponsoring agency, and the ethical standards applied should be no less exacting than they would be in the case of research carried out in that country.
- After scientific and ethical approval in the country of the sponsoring agency, the appropriate ethical clearance committee of the institution in Kenya where the research is to be conducted must satisfy themselves also that the proposed research meets the established scientific and ethical requirements.
- Externally sponsored research designed to develop a therapeutic, diagnostic or preventive product must be responsive to the health needs of Kenya. That means the research to be conducted must address health problems that are important in Kenya.
- The sponsoring agency should agree in advance of the research that any product developed through this research will be made reasonably available to the inhabitants of the community in which research has been conducted or to the whole country at the completion of successful testing.
- Consideration should be given to the sponsoring agency agreeing to maintain health services and faculties established for purposes of the study in Kenya after the research has been completed.
- Such collaborative research should help to develop capacity for similar research in Kenya.

Constituting an Ethical Committee

The purpose of an Ethical Committee (EC) in reviewing biomedical research is to contribute to safeguarding the dignity, rights, safety and well-being of all actual or potential research participants. A cardinal principle of research involving human participants is 'respect for the dignity of persons'. The goals of research, while important, should never be permitted to override the health, well-being and care of research participants. ECs should also take into consideration the principle of justice. Justice requires that the benefits and burdens of research be distributed fairly among all groups and classes in society, taking into account age, gender, economic status, culture, and ethnic considerations.

ECs should provide independent, competent and timely review of the ethics of proposed studies. In their composition, procedures and decision making, ECs need to have independence from political, institutional, professional and market influences. They need similarly to demonstrate competence and efficiency in their work.

ECs are responsible for carrying out the review of proposed research before the commencement of the research. They also need to ensure that there is regular evaluation of the ethics of ongoing studies that received a positive decision.

ECs are responsible for acting in the full interest of potential research participants and

concerned communities, taking into account interests and needs of researchers, and having due regard for the requirements of relevant regulatory agencies and applicable laws.

ECs should be constituted to ensure the competent review and evaluation of all ethical aspects of the research projects they receive and to ensure that their tasks can be executed free from bias and influence that could affect their independence.

ECs should be multidisciplinary and multisectoral in composition, including relevant scientific expertise, balanced age and gender distribution, and laypersons representing the interests and the concerns of the community.

ECs should be established in accordance with the applicable laws and regulations of Kenya and in accordance with the values and principles of the communities they serve.

ECs should establish publicly available standard operating procedures that state the authority under which the committee is established, the functions and duties of the EC, membership requirements, the terms of appointment, the conditions of appointment, the offices, the structure of secretariat, internal procedures, and the quorum requirements. ECs should act in accordance with their written operating procedures.

However, in the course of their duties, ethical review committees (ERCs) will from time to time have some of their decisions on certain medical research proposals challenged, or in certain instances rejected and seen as totally unfair.

For this reason and others that may not be immediately apparent, all ERCs must have within their functional structure, the provision for appeal. During an appeal process, the ERCs need not be unduly biased by their previous decision on a particular research proposal. They should strive to review the appeal as objectively as possible. They should not hesitate to change their previous collective decision if need be.

However, where the appeal is rejected but the aggrieved parties feel that they still have a case, then they should seek leave from the committee to have their proposal(s) reviewed by an extraordinarily constituted Ethical Review Committee if and when deemed necessary by the National Council for Science and Technology. The NCST will be obligated to inform the subordinate ERCs of their decision so that they can also be in the know of what transpired. The NCST-constituted ERC's decision will be final.

It may be helpful to summarize the activities of the EC in a regular (annual) report.

Membership Requirements

Clear procedures for identifying or recruiting potential EC members should be established. A statement should be drawn up of the requirements for candidacy that includes an outline of the duties and responsibilities of EC members.

Membership requirements should be established that include the following:

- the name or description of party responsible for making appointments;
- the procedure for selecting members, including the method for appointing a member (e.g., by consensus, by majority vote, by direct appointment);
- conflicts of interest should be avoided when making appointments, but where unavoidable there should be transparency with regard to such interests.

A rotation system for membership should be considered that allows for continuity, the development and maintenance of expertise within the EC, and the regular input of fresh ideas and approaches.

Terms of Appointment

Terms of appointment should be established that include the following:

- the duration of an appointment,
- the policy for the renewal of an appointment,
- the disqualification procedure,
- the resignation procedure,
- the replacement procedure.

Conditions of Appointment

A statement of the conditions of appointment should be drawn up that includes the following:

- a member should be willing to publicize his/her full name, profession and affiliation;
- all reimbursement for work and expenses, if any, within or related to an EC should be recorded and made available to the public upon request;
- a member should sign a confidentiality agreement regarding meeting deliberations, applications, information on research participants, and related matters; in addition, all EC administrative staff should sign a similar confidentiality agreement.

Offices

ECs should establish clearly defined offices for the good functioning of ethical review. A statement is required of the officers within the EC (e.g., chairperson, secretary), the requirements for holding each office, the terms and conditions of each office, and the duties and responsibilities of each office (e.g., agenda, minutes, notification of decisions). Clear procedures for selection or appointing officers should be established.

In addition to the EC officers, an EC should have adequate support staff for carrying out its responsibilities.

Quorum Requirements

ECs should establish specific quorum requirements for reviewing and deciding on a application. These requirements should include:

- the minimum number of members required to compose a quorum (e.g., more than half the members);
- the professional qualifications requirements (e.g., physician, lawyer, statistician, paramedical, layperson) and the distribution of those requirements over the quorum; no quorum should consist entirely of members of one profession or one gender; a quorum should include at least one member whose primary area of expertise is in a non-scientific area, and at least one member who is independent of the institution/research site.

Independent Consultants

ECs may call upon, or establish a standing list of, independent consultants who may provide special expertise to the EC on proposed research protocols. These consultants

may be specialists in ethical or legal aspects, specific diseases or methodologies, or they may be representatives of communities, patients, or special interest groups. Terms of reference for independent consultants should be established.

Education for EC Members

EC members have a need for initial and continued education regarding the ethics and science of biomedical research. The conditions of appointment should state the provisions available for EC members to receive introductory training in the work of an EC as well as ongoing opportunities for enhancing their capacity for ethical review. These conditions should also include the requirements or expectations regarding the initial and continuing education of EC members. This education may be linked to cooperative arrangements with other ECs in the area, the country, and the region, as well as other opportunities for the initial and continued training of EC members.

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