Chapter 26

Contribution of Biomedical Research Ethics in Public Health Advances

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1. Introduction

The term research refers to a class of activities designed to develop or contribute to generalizable knowledge. Generalizable knowledge consists of theories, principles or relationships, or the accumulation of information on which they are based, that can be corroborated by accepted scientific methods of observation and inference [1]. In the present context "research" includes both medical and behavioral studies pertaining to human health. Generally "research" is usually modified by the adjective "biomedical" to indicate that the reference is to health-related research [1, 2].

Progress in medical care and disease prevention depends upon an understanding of physiological and pathological processes or epidemiological findings, and requires at some time research involving human subjects. The collection, analysis and interpretation of information obtained from research involving human beings contribute significantly to the improvement of human health [3].

Research involving human subjects includes patient care (clinical research) and that undertaken on patients or other subjects, or with data pertaining to them, solely to contribute to generalizable knowledge (non-clinical biomedical research) [4]. Research is defined as "clinical" if one or more of its components is designed to be diagnostic, prophylactic or therapeutic for the individual subject of the research. Invariably, in clinical research, there are also components designed not to be diagnostic, prophylactic or therapeutic for the subject;

examples include the administration of placebos and the performance of laboratory tests in addition to those required to serve the purposes of medical care [5].

Advances in biomedical science and technology, and their application in the practice of medicine, are provoking some anxiety among the public and confronting society with new ethical problems. Society is expressing concern about what it fears would be abuses in scientific investigation and biomedical technology [1, 5]. This is understandable in view of the methodology of biomedical experimental research. Investigation begins with the construction of hypotheses and these are then tested in laboratories and with experimental animals. For the findings to be clinically useful, experiments must be performed on human subjects, and, even though carefully designed, such research entails some risk to the subjects [6]. This risk is justified not by any personal benefit to the researcher or the research institution, but rather by its benefit to the human subjects involved, and its potential contribution to human knowledge, to the relief of suffering or to the prolongation of life [7].

Society devises measures to protect against possible abuses. The first international code of ethics for research involving human subjects — the Nuremberg Code — was a response to the atrocities committed by Nazi research physicians, revealed at the Nuremberg War Crimes Trials [8]. Thus it was to prevent any repetition by physicians of such attacks on the rights and welfare of human beings that human-research ethics came into being. The Nuremberg Code, issued in 1947, laid down the standards for carrying out human experimentation, emphasizing the subject's voluntary consent. In 1964 the World Medical Association took an important step further to reassure society: it adopted the Declaration of Helsinki, most recently revised in 1989, which lays down ethical guidelines for research involving human subjects. In 1966 the United Nations General Assembly adopted the International Covenant on Civil and Political Rights, which entered into force in 1976, and which states (Article 7): *"No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation* ". It is through this statement that society expresses the fundamental, human value that is held to govern all research involving human subjects — the protection of the rights and welfare of all human subjects of scientific experimentation.

In the late 1970s, in view of the special circumstances of developing countries in regard to the applicability of the Nuremberg Code and the Declaration of Helsinki, the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) undertook a further examination of these matters, and in 1982 issued *Proposed International Guidelines for Biomedical Research Involving Human Subjects.* The purpose of the *Proposed Guidelines* was to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the Declaration of Helsinki, could be effectively applied, particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and executive and administrative arrangements [9].

Certain areas of research do not receive special mention in the guidelines; they include human genetic research, embryo and fetal research, and fetal tissue research. These represent research areas in rapid evolution and in various respects controversial.

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The mere formulation of ethical guidelines for biomedical research involving human subjects will hardly resolve all the moral doubts that can arise in association with such research, but the guidelines can at least draw the attention of investigators, sponsors and ethical review committees to the need to consider carefully the ethical implications of research protocols and the conduct of research, and thus conduce to high scientific and ethical standards of research.

Given the different perceptions and priority views in the debate over the value and role of biomedical research, it is believed that the biomedical community must take stock and recommit its efforts to diseases that have a major effect on the population. This requires a re-evaluation of funding priorities, open interactions among researchers, and creating a more effective relations among stakeholders, government, foundations and institutions of higher learning. There is also the need for a shift in paradigm in biomedical research towards poverty related diseases and emerging diseases to reduce the 90/10 gap [6, 30].

2. International declarations and guidelines for ethical framework

The first international document on the ethics of research, the Nuremberg Code, was promulgated in 1947 as a consequence of the trial of physicians who had conducted atrocious experiments on unconsenting prisoners and detainees during the Second World War. The Code, designed to protect the integrity of the research subject, sets out conditions for the ethical conduct of research involving human subjects, emphasizing the human subject's "voluntary consent" to research.

To give the Universal Declaration of Human Rights, adopted by the United Nations General Assembly in 1948, legal as well as moral force, the General Assembly of the United Nations adopted in 1966 the International Covenant on Civil and Political Rights, of which Article 7 states " *No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation.* "

The Declaration of Helsinki, promulgated in 1964 by the World Medical Association, is the fundamental document in the field of ethics in biomedical research and has had considerable influence on the formulation of international, regional and national legislation and codes of conduct. The Declaration, revised in Tokyo in 1975, in Venice in 1983, and again in Hong Kong in 1989, is a comprehensive international statement of the ethics of research involving human subjects. It sets out ethical guidelines for physicians engaged in both clinical and non- clinical biomedical research, and provides among its rules for informed consent of subjects and ethical review of the research protocol [10].

The publication in 1982 of *Proposed International Guidelines for Biomedical Research Involving Human Subjects* was a logical development of the Declaration of Helsinki. As stated in the Introduction of that publication, the Guidelines were intended to indicate how the ethical principles embodied in the Declaration could be effectively applied in developing countries. The text explained the application of established ethical principles to biomedical research

involving human subjects and drew attention to new ethical issues arising in the period that preceded its publication. The present publication, *International Ethical Guidelines for Biomedical Research Involving Human Subjects,* supersedes the 1982 *Proposed International Guidelines.*

CIOMS and WHO have continued to work together to provide ethical guidance for research involving human subjects. One important outcome of this cooperation has been *International Guidelines for Ethical Review of Epidemiological Studies,* published by CIOMS in 1991, intended to assist investigators and institutions as weIl as regional and national authorities in setting and maintaining standards for the ethical review of epidemiological studies [10].

2.1. Fundamental ethical principles

All research involving human subjects should be conducted in accordance with three basic ethical principles, namely respect for persons, beneficence and justice. It is generally agreed that these principles, which in the abstract have equal moral force, guide the conscientious preparation of proposals for scientific studies [11]. In varying circumstances they may be expressed differently and given different moral weight, and their application may lead to different decisions or courses of action. The present guidelines are directed at the application of these principles to research involving human subjects.

2.1.1. Respect for persons

Respect for persons incorporates at least two fundamental ethical considerations, namely:

a) respect for autonomy, which requires that those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination; and b) protection of persons with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse [12].

2.1.2. Beneficence

Beneficence refers to the ethical obligation to maximize benefits and to minimize harms and wrongs. This principle gives rise to norms requiring that the risks of research be reasonable in the light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to safeguard the welfare of the research subjects. Beneficence further proscribes the deliberate infliction of harm on persons; this aspect of beneficence is sometimes expressed as a separate principle, non-maleficience (do no harm).

2.1.3. Justice

Justice refers to the ethical obligation to treat each person in accordance with what is morally right and proper, to give each person what is due to him or her. In the ethics of research involving human subjects the principle refers primarily to distributive justice, which requires the equitable distribution of both the burdens and the benefits of participation in research. Differences in distribution of burdens and benefits are justifiable only if they are based on morally relevant distinctions between persons; one such distinction is vulnerability [13].

"Vulnerability" refers to a substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group. Accordingly, special provisions must be made for the protection of the rights and welfare of vulnerable persons [14].

2.1.4. Research involving human subjects includes the following areas

i. controlled trials of diagnostic, preventive or therapeutic measures in larger groups of persons, designed to demonstrate a specific generalizable response to these measures against a background of individual biological variation

ii. studies designed to determine the consequences for individuals and communities of specific preventive or therapeutic measures; and studies concerning human health-related behaviour in a variety of circumstances and environmentsstudies of a physiological, biochemical or pathological process, or of the response to a specific intervention, whether physical, chemical or psychological- in healthy subjects or patients;

iii. Research involving human subjects may employ either observation or physical, chemical or psychological intervention; it may also either generate records or make use of existing records containing biomedical or other information about individuals who mayor may not be identifiable from the records or information. The use of such records and the protection of the confidentiality of data obtained from those records are discussed in *International Guidelines for Ethical Review of Epidemiological Studies [15].*

Research involving human subjects also includes research in which environmental factors are manipulated in a way that could affect incidentally-exposed individuals. Research is defined in broad terms in order to embrace field studies of pathogenic organisms and toxic chemicals under investigation for health-related purposes.

Research involving human subjects is to be distinguished from the practice of medicine, public health and other forms of health care, which is designed to contribute directly to the health of individuals or communities. Prospective subjects may find it confusing when research and practice are to be conducted simultaneously, as when research is designed to obtain new information about the efficacy of a drug or other therapeutic, diagnostic or preventive modality.

Research involving human subjects need to be conducted only by, or strictly supervised by, suitably qualified and experienced investigators and in accordance with a protocol that clearly states: the aim of the research; the reasons for proposing that it involve human subjects; the nature and degree of any known risks to the subjects; the sources from which it is proposed to recruit subjects; and the means proposed for ensuring that subjects' consent will be adequately informed and voluntary. The protocol should be scientifically and ethically appraised by one or more suitably constituted review bodies, independent of the investigators [16].

3. Consideration of some important ethical guidelines

3.1. Informed consent human participation in clinical research

3.1.1. Guideline 1: Individual informed consent

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 [5, 13].

Informed consent is consent given by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation.

Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research. Informed consent protects the individual's freedom of choice and respects the individual's autonomy [17].

In itself, informed consent is an imperfect safeguard for the individual, and it must always be complemented by independent ethical review of research proposals. Moreover, many individuals, including young children, many adults with severe mental or behavioural disorders, and many persons who are totally unfamiliar with modern medical concepts, are limited in their capacity to give adequate informed consent [17]. Because their consent could imply passive and uncomprehending participation, investigators must on no account presume that consent given by such vulnerable individuals is valid, without the prior approval of an independent ethical-review body. When an individual is incapable of making an informed decision whether to participate in research, the investigator must obtain the proxy consent of the individual's legal guardian or other duly authorized representative [18].

When the research design involves no more than minimal risk- that is, risk that is no more likely and not greater than that attached to routine medical or psychological examination -and it is not practicable to obtain informed consent from each subject, the ethical review committee may waive some or all of the elements of informed consent [19]. Investigators should never initiate research involving-human subjects without obtaining each subject's informed consent, unless they have received explicit approval to do so from an ethical review committee.

3.1.2. Guideline 2: Essential information for prospective research subjects

Before requesting an individual's consent to participate in research, the investigator must provide the individual with the following information, in language that he or she is capable of understanding:

i. that each individual is invited to participate as a subject in research, and the aims and methods of the research; -the expected duration of the subject's participation; -the benefits that might reasonably be expected to result to the subject or to others as an outcome of the research;

ii. any foreseeable risks or discomfort to the subject, associated with participation in the research;

iii. any alternative procedures or courses of treatment that might be as advantageous to the subject as the procedure or treatment being tested;

iv. the extent to which confidentiality of records in which the subject is identified will be maintained;

v. the extent of the investigator's responsibility, if any, to provide medical services to the subject;

vi. that therapy will be provided free of charge for specified types of research-related injury;

vii. whether the subject or the subject's family or dependants will be compensated for disability or death resulting from such injury; and

viii. 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 otherwise be entitled [20].

3.1.3. Guideline 3: Obligations of investigators regarding informed consent

The investigator has a duty to:

1. communicate to the prospective subject all the information necessary for adequately informed consent;

2. give the prospective subject full opportunity and encourage- ment to ask questions;

3. exclude the possibility of unjustified deception, undue influence and intimidation;

4. seek consent only after the prospective subject has adequate knowledge of the relevant facts and of the consequences of participation, and has had sufficient opportunity to consider whether to participate;

5. as a general rule, obtain from each prospective subject a signed form as evidence of informed consent; and

6. Renew the informed consent of each subject if there are material changes in the conditions or procedures of the research [21].

3.1.4. Guideline 4: Inducement to participate

Subjects may be paid for inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research; they may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ("undue inducement"). All payments, reimbursements and medical services to be provided to research subjects should be approved by an ethical review committee [21].

3.1.5. Guideline 5: Research involving children

Before undertaking research involving children, the investigator must ensure that:

i. children will not be involved in research that might equally well be carried out with adults;

ii. the purpose of the research is to obtain knowledge relevant to the health needs of children;

iii. a parent or legal guardian of each child has given proxy consent;

iv. the consent of each child has been obtained to the extent of the child's capabilities;

v. the child's refusal to participate in research must always be respected unless according to the research protocol the child would receive therapy for which there is no medically- acceptable alternative;

vi. the risk presented by interventions not intended to benefit the individual child-subject is low and commensurate with the importance of the knowledge to be gained; and

vii. interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child-subject as any available alternative [22]..

3.1.6. Guideline 6: Research involving persons with mental or behavioural disorders

Before undertaking research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent, the investigator must ensure that:

i. such persons will not be subjects of research that might equally well be carried out on persons in full possession of their mental faculties;

ii. the purpose of the research is to obtain knowledge relevant to the particular health needs of persons with mental or behavioural disorders;

iii. the consent of each 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;

iv. in the case of incompetent subjects, informed consent is obtained from the legal guardian or other duly authorized person;

v. the degree of risk attached to interventions that are not intended to benefit the individual subject is low and commensurate with the importance of the knowledge to be gained; and

vi. interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual subject as any alternative [23].

3.1.7. Guideline 7: Research involving prisoners

Prisoners with serious illness or at risk of serious illness should not arbitrarily be denied access to investigational drugs, vaccines or other agents that show promise of therapeutic or preventive benefit.

3.1.8. Guideline 8: Research involving subjects in underdeveloped communities

Before undertaking research involving subjects in underdeveloped communities, whether in developed or developing countries, the investigator must ensure that:

i. persons in underdeveloped communities will not ordinarily be involved in research that could be carried out reasonably well in developed communities;

ii. the research is responsive to the health needs and the priorities of the community in which it is to be carried out;

iii. every effort will be made to secure the ethical imperative that the consent of individual subjects be informed; and

iv. the proposals for the research have been reviewed and approved by an ethical review committee that has among its members or consultants persons who are thoroughly familiar with the customs and traditions of the community [24].

3.1.9. Guideline 9: Informed consent in epidemiological studies

For several types of epidemiological research individual informed consent is either impracticable or inadvisable. In such cases the ethical review committee should determine whether it is ethically acceptable to proceed without individual informed consent and whether the investigator's plans to protect the safety and respect the privacy of research subjects and to maintain the confidentiality of the data are adequate [25].

3.1.10. Guideline 10: Equitable distribution of burdens and benefits

Individuals or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed. Special justification is required for inviting vulnerable individuals and, if they are selected, the means of protecting their rights and welfare must be particularly strictly applied [26].

3.1.11. Guideline 11: Selection of pregnant or nursing (breastfeeding) women as research subjects

Pregnant or nursing women should in no circumstances be the subjects of non-clinical research unless the research carries no more than minimal risk to the fetus or nursing infant 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 any clinical trials except such trials as are designed to protect or advance the health of pregnant or nursing women or fetuses or nursing infants, and for which women who are not pregnant or nursing would not be suitable subjects [27].

3.1.12. Guideline 12: Safeguarding confidentiality

The investigator must establish secure safeguards of the confidentiality of research data. Subjects should be told of the limits to the investigators' ability to safeguard confidentiality and of the anticipated consequences of breaches of confidentiality [28].

3.1.13. Guideline 13: Right of subjects to compensation

Research subjects who suffer physical injury as a result of their participation are 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 [29]

3.1.14. Guideline 14: Constitution and responsibilities of ethical review committees

All proposals to conduct research involving human subjects must be submitted for review and approval to one or more independent ethical and scientific review committees. The investigator must obtain such approval of the proposal to conduct research before the research is begun. The provisions for review of research involving human subjects are influenced by political institutions, the organization of medical practice and research, and the degree of autonomy accorded to medical investigators. Whatever the circumstances, however, society has a dual responsibility to ensure that [30]

i. all drugs, devices and vaccines under investigation in human subjects meet adequate standards of safety; and

ii. the provisions of the Declaration of Helsinki are applied in all biomedical research involving human subjects.

3.2. Externally sponsored research

3.2.1. Guideline 15: Obligations of sponsoring and host countries

Externally sponsored research entails two ethical obligations:

i. 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.

ii. After scientific and ethical approval in the country of the sponsoring agency, the appropriate authorities of the host country, including a national or local ethical review committee or its equivalent, should satisfy themselves that the proposed research meets their own ethical requirements.

3.2.2. Definition

The term "externally sponsored research" refers to research undertaken in a host country but sponsored, financed, and sometimes wholly or partly carried out by an external international

or national agency, with the collaboration or agreement of the appropriate authorities, institutions and personnel of the host country.

Ethical and scientific review. Committees in both the country of the sponsoring agency and the host country have responsibility for conducting both scientific and ethical review, as well as the authority to withhold approval of research proposals that fail to meet their scientific or ethical standards. Special responsibilites may be assigned to review committees in the two countries when a sponsor or investigator in a developed country proposes to carry out research in a developing country. When the external sponsor is an international agency the research protocol must be reviewed according to its own independent ethical review procedures and standards [31].

Committees in the external sponsoring country or international agency have a special responsibility to determine whether the scientific methods are sound and suitable for the aims of the research, whether the drugs, vaccines or devices to be studied meet adequate standards of safety, whether there is sound justification for conducting the research in the host country rather than in the country of the external sponsoring agency, and that the proposed research does not in principle violate the ethical standards of the external sponsoring country or international organization [32].

Committees in the host country have the special responsibility to determine whether the goals of the research are responsive to the health needs and priorities of the host country. Moreover, because of their better understanding of the culture in which the research is proposed to be carried out, they have special responsibility for assuring the equitable selection of subjects and the acceptability of plans to obtain informed consent, to respect privacy, to maintain confidentiality, and to offer benefits that will not be considered excessive inducements to consent.

In short, ethical review in the external sponsoring country may be limited to ensuring compliance with broadly stated ethical standards, on the understanding that ethical review committees in the host country will have greater competence in reviewing the detailed plans for compliance in view of their better understanding of the cultural and moral values of the population in which the research is proposed to be conducted [33].

3.2.3. Research designed to develop therapeutic, diagnostic or preventive products

When externally sponsored research is initiated and financed by an industrial sponsor such as a pharmaceutical company, it is in the interest of the host country to require that the research proposal be submitted with the comments of a responsible authority of the initiating country, such as a health administration, research council, or academy of medicine or science.

Externally sponsored research designed to develop a therapeutic, diagnostic or preventive product must be responsive to the health needs of the host country. It should be conducted only in host countries in which the disease or other condition for which the product is indicated is an important problem. As a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made reasonably available to the inhabitants of the host community or country at the completion of successful testing. Exceptions to this general requirement should be justified and agreed to all concerned

parties before the research begins. Consideration should be given to whether the sponsoring agency should agree to maintain in the host country, after the research has been completed, health services and facilities established for purposes of the study [34].

3.2.4. Obligations of external sponsors

An important secondary objective of externally sponsored collaborative research is to help develop the host country's capacity to carry out similar research projects independently, including their ethical review. Accordingly, external sponsors are expected to employ and, if necessary, train local individuals to function as investigators, research assistants, or data managers or in other similar capacities. When indicated, sponsors should also provide facilities and personnel to make necessary health-care services available to the population from which research subjects are recruited.[34]. Although sponsors are not obliged to provide health-care facilities or personnel beyond that which is necessary for the conduct of the research, to do so is morally praiseworthy. However, sponsors have an obligation to ensure that subjects who suffer injury as a consequence of research interventions obtain medical treatment free of charge, and that compensation is provided for death or disability occurring as a consequence of such injury. Also, sponsors and investigators should refer for health care services subjects who are found to have diseases unrelated to the research, and should advise prospective subjects who are rejected as research subjects because they do not meet health criteria for admission to the investigation to seek medical care. Sponsors are expected to ensure that research subjects and the communities for which they are recruited are not made worse off as a result of the research (apart from justifiable risks of research interventions) — for example, by the diversion of scarce local resources to research activities. Sponsors may disclose to the proper authorities in the host country information that relates to the health of the country or community, discovered in the course of a study [35].

External sponsors are expected to provide, as necessary, reasonable amounts of financial, educational and other assistance to enable the host country to develop its own capacity for independent ethical review of research proposals and to form independent and competent scientific and ethical review committees. To avoid conflict of interest, and to assure the independence of committees, such assistance should not be provided directly to the committees; rather funds should be made available to the host-country government or to the host research-institution [36].

Obligations of sponsors will vary with the circumstances of particular studies and the needs of host countries. The sponsors' obligations in particular studies should be clarified before research is begun. The research protocol should specify what, if any, resources, facilities, assistance and other goods or services will be made available during and after the research, to the community from which the subjects are drawn and to the host country.The details of these arrangements should be agreed by the sponsor, officials of the host country, other interested parties, and, when relevant, the community from which subjects are to be drawn. The ethical review committee in the host country should determine whether any or all of these details should be made a part of the consent process [36].

4. World medical association declaration of Helsinki

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research. Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries [37].

4.1. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

4.2. Medical research combined with professional care (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient — including those of a control group, if any — should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

4.3. Non therapeutic research involving human subjects (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers, either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related wellbeing of the subject.

5. The phases of clinical trials of vaccines and drugs

5.1. 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.

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.

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 [5].

5.2. Drug development

5.2.1. Phase I

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.

5.2.2. Phase II

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.

5.2.3. Phase III

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.

5.2.4. Phase IV

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 premarketing phases (such as children or the elderly) or to establish a new clinical indication for a drug. Such research is to be distinguished from marketing research, sales promotion studies, and routine post-marketing surveillance for adverse drug reactions in that these categories ordinarily need not be reviewed by ethical review committees

In general, Phase I drug trials and Phase I and Phase II vaccine trials should be conducted according to the articles of the Declaration of Helsinki that refer to non-clinical research. However, some exceptions can be justified. For example, it is customary and ethically justifi-

able to conduct Phase I studies of highly toxic chemotherapies of cancer in patients with cancer, rather than in normal volunteers as prescribed in the Declaration of Helsinki, Article III.2. Similarly be ethically it may be ethically justifiable to involve HIV-seropositive individuals as subjects in Phase II trials of candidate vaccines [37].

Phase II and Phase III drug trials should be conducted according to the articles of the Declaration of Helsinki that refer to "medical research, combined with professional care (clinical research)". However, the Declaration does not to provide for controlled clinical trials. Rather, it assures the freedom of the physician "to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life reestablishing health or alleviating suffering" (Article II.1). Also in regard to Phase II and Phase III drug trials there are customary and ethically justified exceptions to the requirements of the Declaration of Helsinki. A placebo given to a control group, for example, cannot be justified by its "potential diagnostic or therapeutic value for the patient", as Article II.6 prescribes. Many other interventions and procedures characteristic of late-phase drug development have no possible diagnostic or therapeutic value for the patients and thus must be justified on other grounds; usually such justification consists of a reasonable expectation that they carry little or no risk and that t contribute materially to the achievement of the goals of the research [37].

Phase III trials of vaccines do not use "a new diagnostic and therapeutic measure" that offers "hope of saving life, reestablishing health or alleviating suffering" (clinical research). Yet administration of the vaccine is intended to be a benefit to the subject rather than the purely scientific application of medical research carried out on a being" (non-clinical biomedical research). Thus, Phase III vaccine-trials do not conform to either of the categories defined in the Declaration of Helsinki.

6. Advances in biomedical research in 2012

Biomedical research in the United States is a $100 billion enterprise, with approximately 65% supported by industry, 30% by government (predominately the NIH), and 5% by charities, foundations, or individual donors. Although total sponsorship tripled between the mid-1990s and mid-2000s [15], the rate of increase has fallen since 2003 and declined in real (inflation-adjusted) terms since 2007 [3, 17]. The number of new drugs entering human trials has also fallen during the past two decades, especially for new molecular entities and entirely new classes of drugs. In contrast, the number of approvals of medical devices by the Food and Drug Administration (FDA) has increased steadily each year [23]. Driven by demand, total medical spending on devices has increased at a rate that is several times that for health services and twice that for drugs [5, 30].

Since the mid-1990s, the United States has invested approximately 4.5% of its total health expenditures on biomedical research. In contrast, only 0.1% supports research in health services, comparative effectiveness, new care models, best practices, and quality, outcome, or service innovations [37]. This funding will increase to approximately 0.3% from appropriations in 2010 health legislation.

Misconceptions regarding the scientific process are common. Research is costly, capital-intensive, and collaborative. Researchers in both academic and industrial settings require access to much the same information, samples and tissue, instrumentation, and specialized technical skills. They also depend on one another as a source of new ideas. It is a paradox, during this decade of growing scrutiny of ties between academic institutions and companies, that academic investigators value their nonfinancial company ties (with access to technology or research materials) more than personal compensation or support of their laboratory [4, 19]. Moreover, the notion that "pure" (basic) and "applied" (clinical) research exist as distinct activities is belied by their source of sponsorship and the self-reports of how researchers actually spend their time [27]. Such multimode researchers are more productive, as judged by the number of publications, impact factor, success at winning peer-reviewed NIH funding, and number of patents. This reality was cited by a recent U.S. Federal Court opinion overturning the patentability of several genes that predispose women to breast cancer. The court called for patenting practices that favor openness whenever basic discovery is inhibited [3, 20].

Sponsors have sought to improve their research productivity through the NIH Roadmap initiative (especially Clinical and Translational Science Awards) by encouraging alliances between companies and universities, alternative organizational models, and joint investment in costly facilities, such as imaging or gene sequencing [1, 23]. We reviewed the lessons from 70 such alliances from the mid-1960s through 2000 [5]. Although it is too soon to judge the success of the most recent models, in the main, earlier ones have not accelerated the pace of either discovery or clinical application. The sources of difficulty are idiosyncratic, but recurrent problems are a failure at inception to agree on intellectual-property provisions, excessive secrecy, and disagreements over research aims. In our view, the most salient reason for failure is the centralization of authority within large, inherently cautious bureaucracies in government, universities, foundations, and companies. Collectively, such factors inhibit scientists' creativity by disregarding the pluralism of ideas and the diversity of approaches that are necessary for innovation. Conversely, the most successful collaborations have found a balance between external direction and scientists' curiosity. Many of the most experienced observers from government, industry, and academia concur with this viewpoint [25, 31].

Economic forces are also relevant. In the United States, the gain in life expectancy between 1970 and 1990 added $2.4 trillion per year to the gross domestic product by 2000. Moreover, biomedical research bolsters employment, economic development, balance of trade, and exports. Studies from many countries show that investment in new technology of all types is the primary source of economic growth, especially when such investment is made by the private sector [2, 35]. In contrast, in areas in which public spending on technology is dominant, the rates of productivity and growth are lower. The differences are most marked in medical research [15, 44].

Despite these observations, some federal policymakers express doubt that scientific advance is a prerequisite for improved health. They favor predictable, low-cost public health measures and expanded access to basic care during the current decade of austerity [11, 26]. Other policymakers question whether spending on new devices and high-cost bioengineered drugs produce commensurate clinical value [7], 39. Such criticism is driven by estimates that new

technology of marginal benefit (as measured by reduced disease burden or improved longevity) accounts for one half to two thirds of health care inflation in Western countries [31, 46] Even the commercial value of biomedical research is questioned by some companies, as is reflected by their reduced rates of research and development because of unfavorable returns as compared with marketing [1, 17], or mergers and acquisitions [6].

Other observers assert that social, educational, and macroeconomic factors are more important than medicine or public health practice in promoting a population's health [20]. They see technology as a distraction from enlightened social, tax, and regulatory policies. Debate over the goals has already begun [14, 22].

As a consequence, we believe that steps must be taken to reestablish public confidence in researchers and clinicians, along with their institutions. Measures are needed that go beyond those recommended by the Institute of Medicine [3] the Council of Medical Specialty Societies and the National Institute of Health. These reports emphasize remedies that focus primarily on competing interests without dealing with the opportunities. We are concerned that the recommendations overlook the potential for new models to foster productivity[52].

6.1. Seven remedies for consideration

The discontent arising from the current circumstances demands the consideration of sweeping changes in the way we conduct biomedical research. We believe that seven measures should be considered to reconcile competing goals. They require recognition of the multilayered sources of conflict, especially those based on different scientific aims and social values [15].

6.2. Improve data on clinical value

We must develop and apply better objective information about clinical value. This goal implies a higher standard for adopting new devices (including clinical trials similar to those for drugs) and better information on the effectiveness of existing drugs and devices, especially data that are available only from proprietary insurance databases. It is unlikely that provisions for comparative-effectiveness research in the 2010 health care legislation or the changes proposed by the FDA for device approval will be sufficient. New incentives are needed for private and government insurers to disclose clinical data to researchers, along with expanded access to device registries, easier access to data from Medicare and Medicaid, and development of more robust analytical techniques for ascertaining clinical value. Moreover, physicians and surgeons must commit to a new level of objectivity in judging clinical value, while resisting the influence of commercial potential or personal financial interests [13, 48].

6.3. Change the role of teaching hospitals

The roles of academic health centers and teaching hospitals must be modified to improve their ability to conduct early-stage (proof-of-concept) clinical trials. Here, entirely new models for interaction are required, probably involving freestanding independent institutes or autonomous units within academic centers, where patients come specifically for access to such early-stage studies and where the mutual expectations for investigators, companies, and patients

are clear and unambiguous. This change will hasten the divergence between institutions that offer routine care (and that are managed to provide low-cost, reproducible high quality) and those with capability for scientific innovation (where early-stage investigations occur). Making these interactions effective and avoiding the shortcomings of past attempts will require new models of intellectual property, patents, and licensing by moving these aspects farther down the chain of discovery [5]. Two very different approaches should be tried: creating patent pools involving multiple companies and universities [19] and a renunciation of patenting in return for more latitude to conduct high-risk laboratory experimentation and initial clinical trials [26]. It is likely that only some of the 130 academic health centers will choose to undertake such changes.

6.4. Develop new models for collaboration and financing

In asserting the need for an increase of total spending on biomedical research and the need to foster the diversity of scientific approaches, consideration should be given to new models of collaboration and cooperation. Such measures would allow the NIH to concentrate on basic biomedical science and large, multi-institutional projects, where its scale can be most valuable, while providing offset to industry's declining investment in research. These models might include the following [6, 52].

6.5. Create a new class of bonds

States and the federal government might issue bonds to support innovation in biomedical science and health services, with preference given to high-risk research and diseases important to public health. Such bonds have long been used to support athletic facilities, airports, and roads. They provide a mechanism for private investment to meet public needs [18].

6.7. Defer patents to later in the discovery chain

In return for new sources of funding and greater latitude to conduct high-risk research, the new entities would forgo claims to patents or other intellectual property and place positive and negative findings immediately in the public domain.

Emphasizing new incentives, creating new entities, and mobilizing additional funding sources avoid the risk of disrupting productive research relationships currently found in universities, established research institutes, and the NIH. The measures also allow new laboratories to attract the best talent, while providing a route to enhance the productivity of research and its early clinical application [25].

6.8. Establish biomedical innovation trusts

The formation of new nonprofit, public–private partnerships, biomedical innovation trusts, could enable individuals and corporations to receive immediate federal tax credits for contributions to support research in high-priority diseases. Such trusts might be administered by decentralized new foundations or new regional public entities and be directed at particular

diseases, universities, freestanding laboratories, or small companies. Similar tax incentives have been used historically to preserve land, create parks, and build factories [31, 54].

6.9. Use incentives to promote pluralism

To enhance the diversity of scientific approaches and innovation in its application, preference in funding might be given to new research institutes or entities, rather than existing universities or companies.

6.10. Renew professional commitments

All physicians must renew their commitment to professionalism and their duty to their patients. This will not be easy in an age when commercial values are paramount and the competition of the marketplace drives personal and institutional financial decisions. Yet, without such a recommitment, no safeguards will prevent an inexorable loss of trust in our institutions and us. Professionalism, as interpreted today, means not a return to paternalism, but objectivity in judgment on behalf of the patient, with open communication and an absence of bias [37]. It must be translated into action by a blanket proscription of product promotion in any guise.

6.11. Focus on cost-effective targets

We must recognize that new technology creates value to the general economy and has many clinical benefits but that it also usually spurs new clinical costs. Observers who are the most critical of medicine believe we have failed to recognize that historical compromise. In an era in which many favor public-policy goals to ensure a basic level of care for all citizens and a reduction in the rate of increase of aggregate health care spending, the technological imperative will surely be challenged with greater stridency. This requires incentives for researchers to focus on diseases that are common, cannot currently be prevented or effectively treated, are expensive, and have a major effect on the patients' health [2, 13]. Such choices among diseases are onerous but inescapable [47, 60].

6.12. Adopt realistic research goals

We must embrace a new realism about the difficulty of the scientific process and what can (and cannot) be expected from it. We must not overpromise. Such realism will not be popular with patient advocacy groups, the press, politicians, benefactors, or company investors. Each of these groups has a vested interest in overstating their case. Yet to do otherwise runs the risk of eroding the trust on which so much depends. Paradoxically, a commitment to realism may itself have a positive effect on the scientific process by reducing the pressure to promote findings prematurely and by fostering openness [13, 51].

6.13. Redefine the terms of conflict

Finally, we in medicine must recognize that those who have a public health perspective or who see social and economic factors as paramount will not be sympathetic to increasing the

technology-driven momentum of the past 60 years. Inevitably, we face growing conflict over individual choice, access to the latest drug or device, the true cost of technology over a lifetime, perceptions of value, and preferences for competition versus regulation. Such tensions have long been implicit. They are now explicit. Not everyone believes biomedical research is essential [8].

7. Promotion of biomedical research in Sub Saharan Africa (SSA)

7.1. Setting the policies by SSA and stakeholders to prioritize funding for health research

The African heads of state during this decade have embarked on the need for poverty disease control supported by health research. In the Abuja Declaration of 2000, the heads of state pledged their commitments to apply strategies needed to improve on malaria control. They also called for additional resources to stimulate the development of malaria vaccines appropriate for Africa and to provide similar incentives for other anti-malaria technologies [39-41]. In addition the African Union has set a target of allocating 15% of national budget to the health sector, and 2% of health budget to finance health research. The AU countries reportedly agreed to allocate 1% of their countries GDP to research. In its 2008 report, the Global Forum for Health Research only list Liberia to have surpassed the set goal of allocating 15% of its national budget to the health sector by 2003; the report listed Burkina Faso, Central African Republic, Gabon, Gambia, Namibia, Niger and Tanzania to be just over 12%. Before then many of these countries invested very little in health systems. From this report, few low and middle income countries collect and report data on investments in health research [42, 53].

Since the 90s, there are only a few institutions enabling developing country scientists to undertake health research. The situation has since changed significantly, in terms of their allocations. There are currently a number of government agencies that support research, such as World Bank, European Union, World Health Organization (WHO), World Health Organization/Special Programme for Research and Training in Tropical Diseases (WHO/TDR), European Developing Countries Clinical Trials Partnership (EDCTP), Kenya Medical Research Institute (KEMRI), African Malaria Network (AMANET), Drug for neglected Diseases Initiatives (DNDI), National Institute of Health (NIH), Japanese Internatioanl cooperation (JICA), Department for International Development (DFID),), United Nation Development Programme (UNDP), Danish International Development Agency, Dutch Ministry of Foreign Affairs (DGIS), International Development Research Centre (IDRC), Swiss Development Cooperation (SDC), Swedish International Development cooperation agency (SIDA), United State Agency for International Development (USAID) and many other unlisted. Some private philanthropic support to health has been very beneficial in promoting health and reducing the 10/90 gap in sub-Saharan Africa. These include the Bill and Melinda Gates Foundation, EXXON Mobil, Rockefeller Foundation, Wellcome Trust, BH Billiton to name but a few. There are other self financing bodies supporting health research such as the Medical Research Council (MRC) of UK, National Institute of Health (NIH), GlaxoSmithKline (GSK), Pfizer, Norvatis and the United States Department of Defence (DOD) [58-60]

7.2. Major agencies promoting biomedical research and capacity building in Sub-Saharan Africa (SSA)

7.2.1. European Developing Countries Clinical Trials Partnership (EDCTP)

The European Developing Countries Clinical Trials Partnership (EDCTP) was created in 2003, as a European response to the global health crisis caused by malaria. HIV/AIDs and tuberculosis, three poverty-related diseases. EDCTP involves 15 members of the European Union, plus Norway, and Switzerland in partnership with the scientific community and policy makers from sub-Saharan Afica (SSA). The EDCTP started off with a five-year budget of €200 million; member states and the private sector were expected to each contribute a similar sum. EDCTP aims at accelerating the development of new or improved drugs, vaccines and microbicides, against HIV/AIDs tuberculosis and malaria, with a focus on phases II and III clinical trials in SSA. In its work, EDCTP supports clinical trials that combine capacity building and networking, in such a way that the developed human and infrastructure capacity is utilized to conduct multicenter trials, often spanning different SSA countries [52].

The impressive performance of EDCTP is reflected in is 2008 annual report when 21 projects were approved for funding, 27 project contracts worth €54 million were signed. The founding of CANTAM (Central Africa Network of Tuberculosis, HIV/AIDs and Malaria) with EDCTP support, in a research neglected area of Africa is worth mention www.edctp.org. With regard to promoting research and capacity building of researchers and research institutions in SSA, there is no doubt that none compares any closer to WHO/TDR, (the special Programme for Research and Training on Tropical Diseases) which is an independent global programme of scientific collaboration that helps to coordinate support of global efforts to combat major diseases of the poor and the disadvantaged [30].

7.2.2. World Health Organization/special programme for research and training in Tropical Diseases (WHO/TDR),

WHO/TDR was established in 1975, and therefore preceded by a decade and a half the work of the Commission on Health Research for Development, whose members included the founding Director of WHO/TDR. WHO/TDR is soibsired by UNICEF, UNDP, World Bank and WHO; it also receives funding from other agencies across the globe [61].

At the start WHO/TDR restricted its activities to addressing what were by then major neglected diseases, namely malaria, bancroftian filariasis, onchocerciasis, leprosy, leishmaniasis, and African and American trypanosomiasis. Dengue, intestinal helminthes, sexually transmitted infections and tuberculosis were added later. In its early years WHO/TDR made unequaled contributions not only to research on these diseases, but also contributed immensely to capacity building of research leaders in Africa today benefitted from WHO/TDR sponsorship. WHO/TDR also contributed financially and strategically to the development of many new tools and strategies against diseases of poverty. http://apps.who.int/tdr/.

7.2.3. The Kenya Medical Research Institute (KEMRI)

KEMRI established in 1979, operates 10 research centres across the country and employs over 200 national researches and another 500 technical staff. KEMRI has an annual budget of nearly

USD 40 million (of which one-half is Government of Kenya contribution). Several international research teams contribute another 45% KEMRI carries out national ethics review. Major achievements of KEMRI include; national policy basis for control of malaria, tuberculosis, leprosy and leishmaniasis, established surveillance and rapid response systems for major disease outbreaks, improved diagnostics such as KEMRI Hep-cell kit for Hepatitis, particle Agglutination (PA) kit for HIV, and HLA tissue typing techniques [42]

KEMRI successfully collaborated with the Government of Japan to establish global training centres for control of parasitic and infectious diseases. The KEMRI Institute of Tropical Medicine and Infectious Diseases, founded in collaboration with local Jomo Kenyatta University of Agriculture and Technology offers training at MSc and PhD levels. KEMRI founded the African Health Sciences Congress and African Health Journal. www.kemri.org/ (accessed 01/07/12). the progress made by KEMRI since its inception are attributable TO: (i) effective n-s and s-s collaboration (ii) implementation of innovative planning and initiatives, (iii) focused local capacity development and (iv) commitment of the national authorities to strengthen health research and development[23].

7.2.4. African Malaria Network Trust (AMANET)

AMANET has its origins in the African Malaria Vaccine Testing Network (AMVTN) which was established in 1995 with the primary goal of preparing African malaria research institutions to participate in malaria vaccine trials, in 2002, AMANET was registered as a Trust in Tazania and became the Legal successor of AMVTN. This change enabled AMANET to carry out holistic capacity strengthening of trial sites and Centres, and to take on legal responsibilities including sponsorship of trials. The change also signaled the network's commitment and interest in a wider range of malaria interventions, although malaria vaccine development would remain its main focus [29].

The mission of ANANET s to promote capacity strengthening and networking of malaria R&D in Africa, where it has provided institutions with support for essential infrastructure improvement, short-term training to over one thousand health researchers, and uniquely postgraduate degree training in preparation for participation in malaria vaccine development AMANET is funding over 40 projects across SSA, and is well known in Africa for its networks in vaccine trials, bioethics and the Afro-immunoassay network. AMANET also sponsors several blood stage malaria vaccine trials across Africa and has hosted the multilateral initiative on Malaria (MIM) since January 2006 [23]. AMANET Research Ethics capacity strengthens Grant: supported by the Gates foundation where identification of specific gaps in the ethical review process followed by a capacity building programme tailor-made for the identified gaps. A total of 32 ECs have been surveyed in Africa and benefitted from the capacity strengthening sub grants and training activities (www.amanet-trust.org): The south African Research Training initiative (SARETI); based at the University of Kwazulu-Natal and Pretoria University in South Africa, providing training inEthics to African researchers and ERC members. (www.whsph.up.ac.za/sareti/sareti/sareti.htm): The international Research Ethics Network for Southern Africa (IRENSA); based at the University of cape Town, running short term training programmes for mid-career African scientist and embers of Ethics Committees

(www.irensa.org):The Training and Resources in research Ethics Evaluation (TRREE) for Africa, which focuses on development or research ethics educational programmes for e-learning and provision of e-resources [23].

7.2.5. Drugs for Neglected Diseases Initiative (DNDI)

DNDI was established in 2003 is a not-for-profit drug development organization, focused on improving the health and quality of life of people suffering from neglected diseases. DNDI was founded by Médicins Sans Frontières (MSF) with five public sector organizations, viz Kenya Medical Research Institute, Indian Council of Medical Research, Malaysian Ministry of Health, Oswaldo Cruz Fondation, Institute Pasteur France, and WHO/TDR as observer. DNDi support covers basic science, as well as preclinical and clinical research, focusing on human African trypanosomiasis, leishmaniasis, chaga's disease, and malaria. In 2007 DNDi in partnership with Sanofi Aventis, completed trial of a combination of Artesunate with Amodiaquine (ASAQ), as a patent free drug against malaria. DNDi is also responsible for the HAT Platform which addresses Human African Trypanosomiasis (HAT) which is truly a neglected disease; there is very limited clinical research activity geared to improving its treatment or diagnosis, and it is endemic only in remote areas. The HAT platform was therefore established through a partnership of the five most affected countries (the Sudan, Democratic Republic of Congo, Uganda, Republic of Congo, and Angola) in collaboration with DNDi and the Swiss Tropical Institute, and other partners to build and strengthen clinical trial capacity including the search for appropriate diagnostics for HAT. In 2008, the HAT Platform received a US$68.2 million grant from the Bill & Melinda Gates Foundation for this purpose[23].

7.2.6. The Japanese chemical giant Sumitomo Chemical Company

They undertook R&D that led to production of Olyset Nets which incorporate an insecticide (permethrin) into the actual fibers of the net, and releases it slowly over a number of years. Olyset nets are guaranteed to last at least five years; they never need retreatment, are tear-resistant, ash proof, provide maximum ventilation; they inhibit mosquito (Anopheles spp.) biting, they repel, knockdown and kill mosquitoes. Olyset nets were the first long-lasting insecticidal net (LLIN) to be submitted and fully registered by the WHO Pesticide Evaluation Scheme (WHOPES) www.olyset.net/.[23]

In 2003 through a PPP a royalty-free technology transfer was undertaken under which Sumitomo Chemical Company would further develop Olyset nets, which eventually led to setting up a factory in Arusha, Tanzania, that was officially launched in early 2008; it aimed at producing 51 million units during 2009, employing 6000 people in Arusha alone, and supporting over 20,000 others. The factory in Arusha is now a 50/50 joint venture between Sumitomo Chemical Company and A to Z textile Mills, a Tanzania company. Another factory is being set up in Nigeria that will bring global production to more than 60 million nets annually, www.olyset.net/olysetnet/manurfacturinginafrica/ (accessed 06.07.12).

7.2.7.Medical research council UK

The MRC supports and advances medical research in three main ways: through their research facilities, by funding research centres in partnership with universities, and by providing

research grants and career awards to scientists in UK universities and hospitals. Supporting scientists. Around 5,700 research staff are supported by the MRC, either employed directly in our institutes and units or funded through grants and fellowships. It spends about £86m on training awards for postgraduate students and fellows in 2011/12, including those in the MRC's own institutes and units[59].

The MRC expects valuable data arising from MRC-funded research to be made available to the scientific community with as few restrictions as possible so as to maximize the value of the data for research and for eventual patient and public benefit. Such data must be shared in a timely and responsible manner.The MRC believes that data sharers should receive full and appropriate recognition by funders, their academic institutions and new users for promoting secondary research. New studies that result from this data-sharing should meet the high standards of all MRC research regarding scientific quality, ethical requirements and value for money. It should also add recognizable value to the original dataset. Such research is often most fruitful when it is a collaboration between the new user and the original data creators or curators, with the responsibilities and rights of all parties agreed at the outset. Data arising from MRC-funded research must be properly curated throughout its life-cycle and released with the appropriate high-quality metadata. This is the responsibility of the data custodians, who are often those individuals or organisations that received MRC funding to create or collect the data[55].

Research fish (formerly known as MRC e-Val) gathers outputs, outcomes and impacts arising from MRC-funded research. MRC e-Val is an online survey designed to gather feedback from MRC-funded researchers about the results of their work. The aim is to compile accurate information about the outputs of MRC research and to capture impact as it occurs. This information will then be used to communicate the benefits of MRC funding; support evaluations of the economic, social and academic impact of MRC research; and provide evidence for strategy development. Information was sought across the whole MRC portfolio from all MRC researchers that had held MRC support since 2006 (approximately 3000 principal investigators) [60]. A full set of responses was submitted for 2541 Awards. This represents 83% of Awards that were invited to complete MRC e-Val as shown in figure 1.

8. Use of animal in biomedical research

8.1. Using animals in research: Benefits and ethical consideration

In 1780, Jeremy Bentham, an English Philosopher, first initiated the arguments of ethics in the vicinity of protection and treatment against animal by stating that animals should be treated equally as humans and they should not be neglected because they can not speak nor express their emotions [38]. In 1859, Darwin's theory on evolution placed human and animals on the same physical and emotional continuum. From late 19th century till now, a number of animal rights advocates have presented various arguments against animal uses in biomedical research. Using animals in the discovery of scientific knowledge is not only subject to the prosperity of mankind but also that of all species on earth:

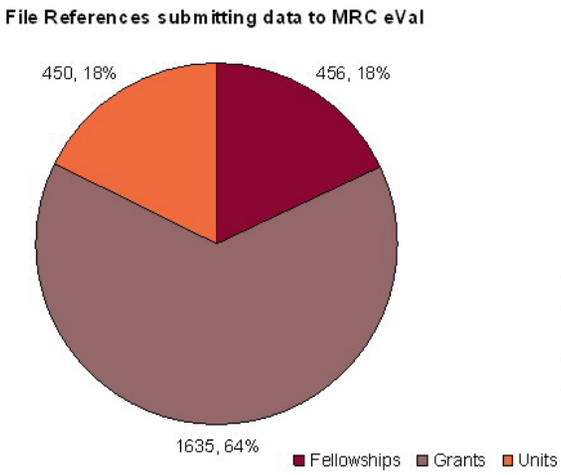

Figure 1. Representation of 83% of Awards that were invited to complete MRC e-Val [51]

The welfare of animals used in research, testing and teaching is affected by a combination of a number of factors. It is the combined effect of biological factors, environmental factors and interactions with the researchers that determine the welfare of animals used for research or teaching purposes [39]. The various factors that affect the welfare of animals used in research have been outlined in table 1.

Biological factors	Environmental factors	Interaction with researchers or teachers
Age if the animals	Ventilation of the room where the animals are kept	Nature of handing (gentle or rough; pain or distress could be caused)
Sex of the animals	Room temperature	Frequency of research procedures could be stressful
Reproductive status of the animals	Relative humidity of the room	Duration of manipulations or procedures (e.g. a class of students using animals in 5-h practical). The same animals may be used by more than one class over a certain period of time
Genetic factors based on the genotype of the animals	Diet during breeding and experimentation	Management practices such as number tags castration, dehorning and tail docking
Stress of the animals	Water availability for the animals	
Physiological/metabolic state of the animals	Light cycle and quality in the room where the animals are kept Noise in the vicinity of the room where the animals are kept Bedding in the cages Size of cages and number of animals per cage Transportation of animal	

Table 1. Types of independent factors that may affect welfare of animals used in research or teaching [46].

One of the strongest grounds of using animals in scientific research is the values of research toward animals and human beings. In the perspective of human health, many diseases such as small pox virus that our forefathers significantly suffered from have now been eradicated or controlled with the aid of biomedical research on animals. The use of animals in research is prevalent because they share at least 200 common illnesses and diseases with humans [38]. Animals are used in research or experimentation in place of human subjects for various reasons. Using animals in research affords the scientist to monitor reactions to stimuli and other variables in complex organs and tissue, while allowing the scientist to minimize environmental variables. Animals are used in scientific research to further science in many arenas. They are used most often in the following cases: Disease Treatment, Prevention, Treatment of Injuries, Basic Medical Testing, and Medical Diagnosis. Animals in research have made possible many scientific breakthroughs that humans benefit from each day such as in; Vaccinations, Anesthesia, Antibiotics, Numerous medical treatments for various diseases. Animals provide the scientist with unique possibilities especially using animals for medical research [39, 40].

When experimenting with new drugs for the treatment of disease it would be virtually impossible to isolate a human the way an animal can be isolated. All mammals share the same systems, there are variants but they are far outweighed by the likeness that humans and animals share. There are just certain testing that can not be accomplished without the use of live organs and tissue. There is no way to duplicate a complex disease in a culture, nor to enable a computer to completely analyze the effects of drugs on a system. Animals play a vital role in medical research [40-42].

8.1.2. Some facts about animal biomedical research

85 % of the animals used in research are rodents - rats and mice that have been bred for laboratory use. Most laboratory tests on animals are simple single type tests - change in diet, drawing a simple blood sample, administering a drug, Animals are given anesthetics if a procedure is going to be invasive in any way. Dogs, cats and non-human primates account for only 3 out of 1000 subjects in experimentation. Humans are still the largest group that is used for research and experimentation and beats out all other lab animals when it comes to testing [44].

A criterion which all scientists must follow is known as the three R's. The three R's in research refer to the following: Refinement, Reduction, and Replacement. Refinement of testing must be arranged so that animal distress is minimal. The scientist must reduce the number of animals used in the experimentation whenever possible and if possible, replace animals with other adequate research methods. There are animal restrictions in place to insure that animals are not used when not necessary[45]. When there are other viable models to conduct research those methods supposed to be used instead of using an animal subject. Only the minimal number of animals is to be used as subjects in an experiment or research project. Unnecessary research and experimentation is considered unethical and use of animals is not supported. The use of animals in research is heavily regulated[46]. The care is mandated through regulatory guidelines and there are heavy damages and fines assessed when these regulations are not followed. The regulations dictate how the animals will be housed and treated to include veterinary care, pain management and other measures to make sure the animals do not suffer

throughout the course of the experiment. The scientist needs to get permission from an ethical committee, which have a full description of the project, before starting any research on animals, to ensure for minimum of suffer among the animals [47-49].

8.1.2.1. Replacement

Animals should be replaced in experiments by less sentient alternatives such as invertebrates or in vitro methods whenever possible.

8.1.2.2. Refinement

If animal experiments can not be avoided protocols should be refined to minimize any adverse effects for each individual animal. Appropriate anaesthesia and analgesia should be used for any surgical intervention. Humane endpoints should be used whenever possible. Staff should be well trained, and housing should be of a high standard with appropriate environmental enrichment. Animals should be protected from pathogens[50, 51].

8.1.2.3. Reduction

The number of animals should be reduced to the minimum consistent with achieving the scientific objectives of the study, recognizing that important biological effects may be missed if too few animals are used. Alternatively, methods should be found to obtain more information from each experiment, thus speeding up the pace of research. This can be achieved by careful control of variation and by appropriate experimental design and statistical analysis [52]..

The use of animals in medical research remains essential. However, in accordance with the law, scientists must avoid using animals wherever possible. If applying for funding for studies involving animals, researchers must give sound scientific reasons for using them and explain why there are no realistic alternatives [52, 55] Around 30 per cent of the research we fund involves animals. Some of the key players involved in one way or another in promoting the implementation of the 3 Rs and the dissemination of information about alternatives to animals in research and teaching are illustrated in table 2.

Organization	**Web site address**
European centre for the Validation of Alternative Methods (ECVAM)	http://ecvam.jrc.it/index.htm(Accessed on 04 June 2009).
Interagency Coordinating Committee on Validation of Alternative methods (ICCVAM) in the USA	http://iccvam.niehs.nih.gov/(Accessed on 04 June 2009).
National interagency Center for the Evaluation of Alternative Toxicological methods (NICEATM) which provides support to the ICCVAM	http://ntp.niehs.nih.gov/ntpweb/index.cfm?objectid =7182FF48-BDB7-CEBA-F8980E5DD01A1E2D (accessed on 04 June 2009)
Norwegian Reference Centre for laboratory Animal Science and Alternatives that maintains the NORINA database containing guidelines on use of animals in	

Organization	Web site address
research as well as audiovisual aids and other teaching materials.	
Alternative to Animal Testing Web Site (Alweb) developed by the John Hopkins Centre for Alternatives to Animal Use	Htt://www.altweb.org (accessed on 04 June 2009)
InterNICHE which promotes humane use of animals in education	www.interniche.org (accessed on o4 June, 2009)
The Netherlands Centre for Alternatives to Animal Use	www.nca-nl.org (accessed on 04 June 2009)
Australian and New Zealand Council for the Care of Animals in Research and teaching (ANZCCART)	anzccart@adelaide.edu.au (Accessed on 04 June 2009).

Table 2. some organizations involved in promoting implementation of the 3Rs [53].

9. Conclusion

Ethical consideration in biomedical research has created a great impact in improving clinical trial research initiatives in both low income economies and industrialized nations. However the lack of scientific expertise and the slow response of scientists, sponsors to ethical questions involving some clinical projects has had a negative effect in the promotion of ethics in biomedical research initiatives. These considerations will require decades of reorientation of our biomedical research efforts. The failure to resolve ethical conflicts be it politically motivated, policy-related, or personal (scientist bias), claims of legitimately competing priorities has limited progress in biomedical research and has encouraged new regulatory constraints in new product development. The IRBs should therefore build a solid working framework, advance capacity building strategies and implement a synergy working platform to promote biomedical and clinical research geared to promote science contribution to human development.

It is also of importance to recognize the contribution of animals used in biomedical research to the good health of humans as well as animal, as moral agents, human beings should always make efforts to ensure that animals are treated humanely in research and teaching.

Efforts should be made to uphold the principles of 3Rs, which ensures that researchers should replace animals with other alternatives whenever possible, and if not possible then the number of animals used should be reduced to the minimum possible sample size as regards to the required statistical power, and refine the methodologies in order to minimize any harm that may be caused by the experimental procedures. It is a welcome idea for the creation of animal ethics committee, and the development of credible national ethics and legal framework, capacity building of research on humane treatment of experimental animals and dialogue among the different stakeholders concerned with the welfare of animal implicated in research.

Special effort have been made to identify some key players in the promotion of biomedical research and their responsibilities, and all the guidelines indicated in this study are intended to protect research participants, and uphold the fundamental ethical principles.

Although there are many action put in place to resolve the 10/90 gap and much has been achieved, the gap still persist. There is the need for more investments towards strengthening of capacities in health research and institutions in sub-saharan Africa to bridge the 10/90 gap. There is also the need to find better ways of translating health research results conducted within the framework of fundamental ethical principles into action and policy implementations.

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References

[1] Barrett DH, Bernier RH, Sowell AL .Strengthening public health ethics at the centers for disease control and prevention.; Centers for Disease Control and Prevention Public Health Ethics Committee Steering Group. Journal Public Health Management Practice. 2008; 14(4):348-53.

[2] Beauchamp, T.L., Childress, J.F. Principles of Biomedical Ethics, 5th edition Oxford University Press. 2001.

[3] Beauchamp, T. The concept of paternalism in biomedical ethics. In Beauchamp, T. Standing on principles. New York: Oxford University Press 2010; pp. 101–119).

[4] Beecher, H.K. Ethics and Clinical Research. New England Journal of Medicine. 1966. 274, 1354.

[5] Benatar, S. R. (2002). Reflections and recommendations on research ethics in developing countries. Social Science and Medicine, 54(7), 1131–1141.

[6] Bernheim, R.G., Melnick, A. Principled leadership in public health: integrating ethics into practice and management. Journal Public Health Management Practice.2008; 14(4):358-66.

[7] Beskow, L.M., Namey, E.E., Cadigan, R.J., Brazg, T., Crouch, J., Henderson, G.E., Michie M., Nelson, D.K., Tabor, H.K., Wilfond, B.S. Research participants' perspectives on genotype-driven research recruitment. Journal of Empirical Research for Human Research Ethics.2011; 6(4):3-20.

[8] Bhutta, Z.A., (2002). Ethics in international health research:a perspective from the developing world. Bulletin WHO, 80:114-120.

[9] Buchanan, D. R. Autonomy, paternalism, and justice: Ethical priorities in public health. American Journal of Public Health, 2008; 98(1), 15.

[10] Cadigan, R.J., Michie, M., Henderson, G., Davis, A.M., Beskow, L.M. The meaning of genetic research results: reflections from individuals with and without a known genetic disorder.J Empirical Research and Human Research Ethics. 2011; 6(4):30-40.

[11] Chilengi, R. An ethics perspective on responsibilities of investigators, sponsors and research participants. Acta Tropica, 2009; 112S:S53-S62.

[12] Council for International Organizations of Medical Sciences (CIOMS) .International Guidelines for Biomedical Research Involving Human Subjects. Geneva.CIOMS; 2002; pp.112.

[13] Department of Health. Tackling health inequalities: 10 years on, Publication No. 291444, London: Crown.2009.

[14] Emanuel, E., Wendler, D., Killen, J., and Grady, C. What makes clinical research in developing countries ethical? the benchmarks of ethical research. The Journal of Infectious Diseases,2004; 189(5), 930–937.

[15] Fineberg, H.V.Shattuck Lecture. A successful and sustainable health system--how to get there from here. North England Journal of Medicine. 2012; 15; 366(11):1020-7.

[16] Gitau-Mburu, D. Should public health is exempt from ethical regulations? Intricacies of research versus activity.East Africa Journal of Public Health. 2008; (3):160-2.

[17] Gollust, S.E., Baum, N.M., Jacobson, P.D. Politics and public health ethics in practice: right and left meet right and wrong. Journal of Public Health Management Practice. 2008. 14(4):340-7.

[18] Huddle TS. Honesty is an internal norm of medical practice and the best policy.American Journal of Bioethics.2012; 12(3):15-27.

[19] Hyder, A.A., Merritt, M., Ali, J., Tran, N.T., Subramaniam, K., Akhtar, T. Integrating ethics, health policy and health systems in low- and middle-income countries: case studies from Malaysia and Pakistan. Bulletin World Health Organization.2008; 86 (8): 606-611.

[20] International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice,1996. Available freely on the websites and other sources.

[21] Jefferson, A.L., Carmona, H., Gifford, K.A., Lambe, S., Byerly, L.K., Cantwell, N.G., Tripodis, Y., Karlawish, J. Clinical Research Risk Assessment among Individuals with Mild Cognitive Impairment. American Journal of Geriatrics and Psychiatry. 2012; 30. 12-30.

[22] Joyce, G.F., Carrera, M.P., Goldman, D.P., Sood, N., Physician prescribing behavior and its impact on patient-level outcomes.American Journal of Management Care. 2011; 1;17(12):e462-71.

[23] Kilama, W.L. The 10/90 gap in sub-Saaran Africa: Resolving inequities in health Research. Acta Tropica 2009; 112S:S8-S15.

[24] Kost, R.G., Lee, L.M., Yessis, J., Coller, B.S., Henderson, D.K. Assessing research participants' perceptions of their clinical research experiences; Research Participant Perception Survey Focus Group Subcommittee. Clinical Translational Science.2011; 4(6): 403-13.

[25] Krech R.Working on the social determinants of health is central to public health. Journal Public Health Policy.2012; 33(2):279-84.2012.10.

[26] Lavery, J.V., Harrington, L.C., Scott, T.W. Ethical , Social, and Cultural considerations for the site selection for research with genetically modified mosquitoes. American Journal of Tropical Medicine and Hygiene, 2008; 79 (3), 312-318.

[27] London AJ, Kimmelman J, Carlisle B . Research ethics. Rethinking research ethics: the case of post-marketing trials. Science 2012; 4; 336(6081):544-5.

[28] Nicholas, J. Next steps in clinical trial redesign. Journal of National Cancer Institute. 2012; 18;104(2):90-2.

[29] Nuffield Council on Bioethics. Public health: Ethical issues. Cambridge: Cambridge Publishers, 2007, p212.

[30] Nyika, A., Kilama, W., Chilengi, R., Tangwa, G., Tindana, P., Ndebele, P., Ikingura, J., Composition, training needs and independence of ethics review committees across

Africa: are the gate-keepers rising to the emerging challenges? Journal of Medical Ethics, 2009: 35, 189-193.

[31] Omonzejele, P.FIs the codification of vulnerability in international documents a sufficient mechanism of protection in the clinical research ethics context? Medical Law. 2011: 30(4):497-515.

[32] Reiter-Theil, S., Agich, G.J., Research on clinical ethics and consultation. Introduction to the theme. Medical Health Care Philos. 2008; 11(1):3-5.

[33] Sade, R.M. Why physicians should not lie for their patients. American Journal of Bioethics. 2012:12(3):17-9.

[34] Tangwa, G.B., Ethical principles in health research and review process. Acta Tropica, 2009. 112S:S2-S7.

[35] Thomas, J.C., MacDonald, P.D., Wenink, E., Ethical decision making in a crisis: a case study of ethics in public health emergencies : Journal Public Health Management Practice; 2009. 15, (2):E16-21.

[36] Wikler, D., and Brock, D. W. Population-level bioethics: Mapping a new agenda. In Dawson, A., and Verweij, M, Ethics, prevention, and public health, 2007. p. 78. New York: Oxford University Press.

[37] World Medical Association Declaration of Helsinki, Available at http://www.wma.net/e/policy/17-c-e.html. Ethical principles for Medical Research Involving Human Subjects. 52nd WMA General Assembly, Edinburgh, Scotland. www.dndi.org (accessed 04.08.12).

[38] Blakemore C: Misguided thinking on animals. Nature 1989;339:414.

[39] Bowman P: Institutional animal care and use committee review of wildlife field research. Lab Animal 1989;18:28-30.

[40] Britt D: Ethics, ethical committees and animal experimentation. Nature 1984;311:503-506.

[41] Dawkins MS: From an animal's point of view: Motivation, fitness, and animal welfare. Behav Brain Sci 1990;13:1-61.

[42] Duggan JM: Resource allocation and bioethics. Lancet 1989;1:772-773.

[43] Fox MW: A call for common understanding of animal welfare, animal rights, and animal well-being. J Am Vet Med Assoc 1990;196:832-833.

[44] Good RA: The value of animal research. Science 1990;248:538

[45] Harvard University's Office of Government and Community Affairs: The Animal Rights Movement in the United States: Its Composition, Funding Sources, Goals, Strategies and Potential Impact on Research. Clarks Summit, PA, Society for Animal Rights, Inc., 1982..

[46] Hoff C: Immoral and moral uses of animals. New England Journal of Medicine 1980;302:115-118.

[47] Lutts RH: The Nature Fakers: Wildlife, Science and Sentiment. Golden, CO, Fulcrum Publishing, 1990.

[48] Markell DL: The case for revising our laws on animal experimentation. International Journal for the Study of Animal Problems 1981;2:87-95.

[49] Meischke HRC, Begbie RA: Philosophical and moral aspects of the use of animals in experimentation. Australian Veterinary Association Yearbook 1981;232-237.

[50] Miller HB, Williams WH: Ethics and Animals. Clifton,NJ, Humanic Press, 1983..

[51] National Research Council: Use of Laboratory Animals in Biomedical and Behavioral Research. Washington, D.C., National Academy Press, 1988..

[52] Thelestam M, Gunnarsson A: The ethics of animal experimentation. Proceedings of the second CFN symposium held in Stockholm, Sweden, August 12-14, 1985. Acta Physiologica Scandinavica 1986;128:269pp.

[53] National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research subjects (NCPHSBBRS). Protection of Human Subjects: Institutional Review Boards. Fed Regist; 1978; 43:231-561.

[54] ICH-GCP E6. International Conference on Harmonization Guidance: Good Clinical Practices. Global Medical Education and Development. 1997. Available at http// www.icr-global.org.

[55] Lavery VJ, Grady C, Wahl RE, Emmanuel JE. Ethical issues in International Biomedical Research: A case book, Oxford University Press, 2007.

[56] United Nation. Universal Declaration of Human Rights. Available at http:// www.un.org/en/document/udhr/.1948.

[57] World Health Organization. Operational Guidelines for ethics committees that review biomedical research, available at http://apps.who.int/tdr/svc/publications/training-guideline-publications/operational-guidelines-ethics-biomedical-research, 2000.

[58] Shemdoe GS. Introduction to intellectual property rights for investigator in health research and institutional intellectual property policy. Acta Tropica 2009; 112S:S80-S83.

[59] Kilama W. From Research to control: Translating research findings into health policies operational guidelines and health products. Acta Tropica, 2009; 112S:S91-S101.

[60] World Medical Association. Declaration of Helsinki. Ethical principles for research involving human subjects. Adopted by the 52 nd WMA General Assembly, Seoul, South Korea, 2008.

[61] Amir JA. Research and Legal Liability. Acta Tropica, 2009;112S:S71-S75).

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