Ethics Guidelines for Health Research Involving Human Participants in Zimbabwe

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1 THE IMPORTANCE OF ETHICS

1.1 Introduction

Zimbabwe provides a unique and highly attractive research environment, with its mix of skills, expertise and infrastructure and its developing-country burden of disease. This environment has attracted many researchers. The clinical trial industry in Zimbabwe reportedly increased in complexity and by size, growing by approximately 70% between 2000 and 2007. Increasing research activity, competition in research and the attractive research environment may sometimes result in dishonest and fraudulent practice. The need for a broad statement on ethics and health research in Zimbabwe is therefore a necessity.

Progress in science has resulted in the development of innovative medical treatments, many of which could be beneficial to people living in low-income countries. In recent years, Zimbabwe has become a sought-after venue for conducting health research that could lead to the development of some of these innovative new medical treatments. The scientists who conduct the research are bound by the requirements of evidence-based medicine.

Nevertheless, in the course of the work that is done, the human rights of poor and marginalized people and those who do not understand the processes of research are frequently violated. This is of grave concern to all Zimbabweans. In particular, we must provide adequate protection for people who are especially vulnerable as a result of poverty or who might currently be underserved.

Research ethics are bound by various national and international codes and guidelines, supplemented by the *Universal Declaration of Human Rights (1948).* In terms of these documents, all research involving human participants should be conducted in accordance with three basic ethical principles, namely: respect for human beings; beneficence, and justice.

These guidelines, entitled *"Ethical Guidelines for Health Research Involving Human Participants in Zimbabwe"* contain our national policy on the ethical practice of research, in accordance with our specific national needs. They establish mechanisms for the ethical review of studies conducted on human participants, and draw attention to the need to consider the ethical implications of professional action. In this way we are endeavouring to inculcate high professional standards in regard to both human attitudes and quality of research.

1.2 Key Texts

Much work has been done internationally to develop guidelines for the conduct of health research in human participants. Key texts, which should be essential reading and reference sources for Zimbabwean based researchers, are listed in ***Appendix A*** with some additional references of interest.

1.3 Scope of the Guidelines

The term "research" refers to a class of activity 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. In the present context "research" includes both medical and behavioural studies pertaining to human health. Usually "research" is modified by the adjective "biomedical" to indicate its relation to health.

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 involves human participants. The collection, analysis and interpretation of information obtained from research involving human beings contribute significantly to the improvement of human health.

Research involving human participants includes:

a. research of a physiological, biochemical or pathological process, or of the response to a specific intervention – whether physical, chemical or psychological in healthy participants or patients;
b. 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;
c. studies designed to determine the consequences for individuals and communities of specific preventive or therapeutic measures; and
d. Studies concerning human health-related behaviour in a variety of circumstances and environments.
e. Studies may also either generate records or make use of existing records containing biomedical or other information about individuals who may or 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 these guidelines
f. The research may be concerned with the social environment, manipulating environmental factors in a way that could affect incidentally-exposed individuals.
g. Research may also include use of stored human tissue and biological samples in repositories and/or bio-banks. The collection, storage and use of such specimen identifiable or not is also discussed in these guidelines

   This list is not exhaustible, as research becomes more and more complex new categories may emerge.

These guidelines do not incorporate reference to the work of Traditional Medicines/Health Research, since this is the one of the latest branches of healing to be given official recognition in Zimbabwe. A separate guideline is being developed in collaboration with the Traditional Medicines Council and Department in the Ministry of Health and Child Welfare. In future, it will be appended into an updated version of these guidelines.

1.4 Ethics and Research

To be ethical, all health research on animals and on human participants must be scientifically sound. Ethics are as important as scientific considerations when reviewing a research project. A Zimbabwean based ethics committee must review the ethical and scientific rigor of all research projects.

1.5 Ethics and Legislation.

In due course Zimbabwean Institutional Review Boards will receive guidance from National Ethics Committee (MRCZ). The Role of the MRCZ will be to promote, accredit and monitor compliance of IRBs within relevant legislation and regulations, ethical guide lines and standard.

(The Government Notice No. 225 of 1974 is being updated to be in tandem with the international standards in research ethics)

1.6 Applicability of these Guidelines

The principles outlined in this document should guide all research involving animals and human participants in any discipline relating to health. Zimbabwean ethics committees are encouraged to adopt these principles to guide their efforts in assessing all health research projects. All health research in Zimbabwe, including research undertaken by other national bodies, should be participant to these Guidelines. Compliance with these standards and with other national and international scripts reassures the public that the rights, safety and well being of study participants are protected.

These guidelines are intended for use by investigators, ethical review committees, administrators, health-care practitioners, policy-makers, and community representatives. Ethics Committees should be especially vigilant when considering research proposals involving vulnerable populations like children, pregnant and nursing women, persons with mental illnesses or handicaps, members of communities unfamiliar with medical concepts, and persons with restricted freedom, such as prisoners. Similar vigilance should be applied to proposals for invasive research that has no direct benefit for its participants.

2. GENERAL ETHICS PRINCIPLES

(To have true understanding of the overarching and universal ethical principles this section was extracted as it is from the Belmont Report- Appendix B).

The expression "basic ethics principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect for persons, beneficence and justice.

2.1 Respect for Persons

Respect for persons incorporates at least two ethical convictions: first, that, individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy. An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2.2 Beneficence

Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation.

Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms. The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

2.3 Justice

Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to

distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed.

These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit. Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients.

Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project; long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

3. GUIDING PRINCIPLES

The purpose of this statement on ethical principles for health research in Zimbabwe is to identify good, desirable and acceptable conduct, to protect the welfare and rights of research participants, and to reflect the basic ethical values of beneficence, justice and respect for persons. Health researchers must conform to the following ethical principles and values, which must underscore all health research activities in Zimbabwe.

3.1 Respects and Dignity

Respect for the dignity, safety and well-being of participants should be the primary concern in health research involving human participants. Culture, language, beliefs, perceptions, and customs must all be considered.

3.2 Relevance

Researchers in Zimbabwe have ethical responsibility to ensure that their research is relevant both to the broad health and development needs of the country and to the individual needs of those who suffer from the diseases and concerns under study. The findings of the research must be translatable into mechanisms for improving the health status of Zimbabweans.

3.3 Scientific Integrity

In addition to fulfilling a need and being of value, the research proposed must demonstrate sound methodology and a high probability of providing answers to the research questions posed. The research protocol must show knowledge of relevant literature, derived from a systematic review of that literature and, where appropriate, from laboratory and animal studies. Moreover, research methods and results must be open to peer review and scrutiny.

3.4 Investigator Competence

A suitably qualified investigator should conduct the study. The investigator's competence is assessed mainly by technical competence, which includes research competence, and is itself assessed in terms of education, knowledge, certification and experience. Compassion and empathy are among the characteristics required of a technically competent researcher. A proper clinical and research environment, encompassing good research mentoring, provides this. In all cases the local principal investigator must be a Zimbabwean-based researcher; that is, one who is ordinarily permanently resident in Zimbabwe.

3.5 Principal Investigator Responsibilities

The Principal Investigator (PI) is the one who submits an application to the MRCZ.
Principal Investigators bear full responsibility for the scientific and ethical aspects of their study, and are the means of communication with the ethics committee while obtaining approval. Once a study is in progress all reports of adverse events and management issues dealt with by the sponsoring company should be transmitted to the ethics committees, ideally through the Principal Investigator, who should be fully informed of these issues. In addition, a system to ensure tracking of all research will be set up through the MRCZ and local ethics committees. This will involve each study being allocated a national study number and a position in the national database. It is envisaged that ethics committees will be allocated cohorts of notification numbers.

3.6 Informed Consent

Informed consent must be obtained from research participants before the research can begin. Both written and verbal informed consent must be obtained, unless there are good reasons to the contrary, such a situation of coma, emergency, or mental incapacity. Prior approval of the ethics committee must be obtained in all situations in which it is justifiable to initiate research without the informed consent of the participant. Verbal consent, where the participant is illiterate, should be obtained in the presence of a literate witness who should verify in writing, duly signed, that informed verbal consent was obtained. Informed consent means that a participant has been informed about the risks and benefits of the research, understands such risks and benefits and is able to give consent to participation, without coercion, undue influence or inappropriate incentives.

In Zimbabwe, researchers must be particularly aware of the vulnerability of prospective participants in terms of access to health services and education levels. Research details must be provided in a clear, simple and culturally appropriate manner. If a participant lacks capacity to exercise an informed choice to participate, an appropriate person to make the choice for them must be identified by the investigator. A participant is free at any time to withdraw consent to further involvement in the research, without having to face any unfair negative consequence or disadvantage. The following essential elements must be understood before a participant is capable of giving informed consent.

- That consent is being given to participate in research;
- The purpose of the research;
- The expected duration of the participant's involvement;
- A description of the procedures to which the participant will be subjected, including any experimental procedures that are innovative and have not been used in medical practice

Prospective participants should be helped to arrive at an informed decision by, for instance, use of appropriate language, selection of a non-threatening environment for interaction and the availability of peer counseling. Participants may find information about the following points useful.

- The investigators' qualifications;
- Explanation of participants' responsibilities;
- Description of foreseeable risks or discomforts;
- Description of benefits to the participants or to others, both during and after the research;
- Disclosure of alternative procedures or courses of treatment;
- Description of the extent to which confidentiality will be maintained;
- Statement that sponsors of the study may be able to inspect research records;
- Statement that the research has been approved by an accredited research ethics committee;
- Contact details of research ethics committee representatives;
- Explanation as to whether compensation will be given for research-related injuries;
- Explanation as to the consequences of injury, including medical treatments;
- Explanation of whom to contact in the event of research-related injury.

Investigators must assure potential participants that participation is voluntary, and that refusal to participate, or a decision to discontinue participation, will not involve any form of penalty. The approximate number of participants should be disclosed. Details of treatment must be supplied and, where appropriate, the possibility of random assignment to various treatments or procedures must be made clear. The nature of experimental and control groups must be explained, as well as circumstances that might lead to the termination of participation.

Unforeseeable risks obviously cannot be foreseen, but participants must be told the nature and extent of risks – including financial risks – attendant on participation. Participants must be made

aware of their right to be informed of relevant new findings, and of the consequences of their withdrawal from research. They should know, too, whether the investigator might terminate participation.

The above points may be regarded as essential elements of informed consent, and all should be incorporated in an Informed Consent Form or document.
Informed consent is a vital requirement in ethical conduct, and is valid only when it is obtained without deceit or misrepresentation. The informed consent requirements are not intended to pre-empt the laws of the country, which may require that additional information be provided to the participants.

The moral duties of the medical practitioner or other investigator are in no way limited by these requirements.

3.7 Privacy and Confidentiality

In its simplest form privacy is concerned with access to personal records, while confidentiality refers to the use of personal information once it has been disclosed. A participant's right to both privacy and confidentiality must be protected. The researcher must ensure that 'where personal information about research participants or a community is collected, stored, used or destroyed, this is done in ways that respect the privacy or confidentiality of the participants or the community and any agreements made with the participants or community.

3.8 Inclusion and Exclusion Criteria

The selection, recruitment, exclusion and inclusion of research participants must be just and fair, based on sound scientific and ethical principles. No person may be inappropriately or unjustly excluded on the basis of race, age, sex, sexual orientation, disability, education, religious beliefs, pregnancy, marital status, ethnic or social origin, conscience, belief or language.

3.9 Risk and Benefits

A risk/benefit analysis of the study should precede the research itself. Risk/benefit analysis should take full notice of benefits and harms beyond the duration of the research, particularly in the case of chronic life-threatening conditions. Alternative ways of providing benefits to the participants might be available. The principal investigator has the ethical duty to exclude participants who might be placed at undue risk.

3.10 Publication of Results

Investigators have an obligation to disseminate research results, whether positive or negative, in a timely and competent manner. This is particularly important in clinical trials, where investigators are duty bound to ensure that findings are made public for all outcomes assessed. It is, however, important that the release of research findings be done in an ethical manner, to ensure that false expectations are not raised in a vulnerable population. Research results should not be prematurely released or published, or unreasonably delayed. It is advisable that the main results should be disseminated, using appropriate communication formats, to the participants and other interested members of the communities in which the study was conducted.
Results of a study, whether sponsored by government or industry, should be the intellectual property of the investigators, not the sponsor, and all results that have scientific merit should be published.

Requests to withhold findings, to change or tone down the content of a report are not acceptable in good ethical practice. However, sponsors or stakeholders should be afforded the opportunity to comment on research findings prior to publication, without any entitlement to veto, change the conclusions, or unreasonably delay publication of results.

In collaborative research with pharmaceutical or other companies, the conditions of publication should be spelt out clearly in the protocol. Research ethics committees should be satisfied that there is no interference with the right to publish results.

3.11 Conflict of Interest

A researcher must disclose the sources and extent of funding to the research participants, the ethics committee and, where appropriate, to the regulatory authority. Commercial affiliations or financial interests at the time of proposing and reporting the research must also be disclosed.

3.12 Safety Monitoring

Safety monitoring of research activities is imperative, particularly in a clinical trial. This involves the prompt reporting of serious adverse events, including post-study events. It is the researcher's responsibility to ensure that adequate provisions are made to deal with any adverse event. The processes for this should be outlined in the research protocol.

3.13 Multi-Centre Studies

The number of multi-centre clinical trials and studies being undertaken in Zimbabwe has increased dramatically in recent years. Prior to commencement of a study, approval should be obtained from the local research ethics committee. Designs should be appropriate to the local setting and particular modifications should be made to the local study when required, in the case of inclusion and exclusion criteria, for instance. It is unacceptable for developed-country participants to be offered better standards of care than are offered to Zimbabwean participants in a similar study. In particular, when Zimbabwe is chosen for a trial or study that has not been undertaken in the country of origin, an explanation should be sought as to why this is the case. In terms of study design, special attention should be paid to the sampling strategy. Other issues in international studies include financing of the study, the appropriateness of incentive packages to research participants and remuneration packages for investigators.

3.14 Multinational Collaborative Research

The challenge to international research ethics is the development of universal rules for research at a time when health care is being delivered within very different health care systems (even within a single country) and in a multicultural world in which people live under radically different economic conditions. Variable trajectories of emancipation of individuals from community have also given rise to a wide spectrum of self-image, what it means to be ill and how health care systems should be structured. With recognition of the role of social conditions in shaping the world, and how privileged people view the world and themselves, comes the realisation that research cannot be considered in isolation. Medical research, health care, conditions of life around the world and how humans flourish may seem disparate, but all are interdependent. The global perspective adds complexity to the task of crafting universal guidelines for research ethics. It is necessary to ensure that:

- Benefits accrue to participants in the host country. Research with benefits limited to the sponsoring country is exploitative and unacceptable;
- The potential benefits of research considerably outweigh potential risks or harms to vulnerable individuals and communities;

- Research is non-exploitative and in the best interests of the research participants and their community;
- Groups already vulnerable are provided with improved access to research – in all countries;
- Research participants are encouraged to participate in planning and conducting studies;
- Research in developing countries is linked to capacity-building in health care, and to economic and educational empowerment to promote the delivery of health care and progress generally in the host country;
- Consideration is given to the risks and potential benefits to research participants, in proportion to the magnitude of benefit to sponsors;
- Honest efforts are made to translate research findings into components of accessible care in the community being researched;
- Conflicts of interest are avoided;
- Research protocols are modified to suit the situation in local communities;
- Publication of articles should be inclusive of investigators as authors from both host and sponsoring countries where appropriate contributions have been made.

3.15 Standard of care

In the past 'standard of care' has not been clearly defined. It has generally been assumed to refer to 'drug treatments'. This is inadequate and the definition should be clarified and extended beyond consideration of drugs to consideration of other aspects of care that are either under the control of investigators or that could be influenced by them. The provision of equal standards of medical care to all during research is a requirement for demonstrating equal respect for the dignity of research participants. An adequate definition of 'standard of care' should include:

- Equal respect for the human dignity of all participants irrespective of their location;
- Obtaining informed consent in the research participants' home language, coupled with an understanding of their world-view or value system;
- Provision of equal general care facilities, through access to the same modern technology and other external factors that may have contributed to the 'best proven' use of the drugs elsewhere, such as medications and care for other diseases, and access to advice and support to sustain compliance;
- The same follow-up facilities for research participants after completion of the study and the same access to ongoing care.

It is suggested that in determining the standard of care that should apply to research in developing countries it is not justifiable to be selective and choose only one aspect of a standard of care – such as drug treatment – without giving adequate reasons for such choice. In the absence of justification, the choice of only one of the elements of the standard of care may seem arbitrary. It may not be possible to meet all requirements in any developing country, but there are bound to be aspects of treatment or intervention that can be met immediately – those that are under the direct control of the investigator. It is suggested, then, that researchers from highly resourced countries bear some responsibility to promote better health care and research conditions by garnering additional support from partners in their own countries.

3.16 Placebo-controlled studies

Research must be designed so that the foreseen benefits and risks to the research participants are equivalent in all aspects. The choice of intervention (placebo or some treatment) to administer to participants in the control arm of a study may require the balancing of many factors, but the welfare of participants must be paramount. The choice of control should be justified as part of the research

protocol. Ethics review committees should verify that the control is appropriate, does not impose risks that are unreasonable in relation to the anticipated benefits, and that placebo controls are not employed without compelling justification. The research design should have the potential to yield scientifically valid results relevant to the population in which the research takes place.

Justifications for using a placebo in the control arm are that:

- No treatment or intervention is accepted as being effective for the condition;
- Treatments or interventions are accepted as being effective for the condition, but the use of a placebo will not result in more than minimal adverse effects that are entirely reversible;
- Treatments or interventions are accepted as effective for the condition, but no scientifically justifiable control option, other than a placebo, meets the objective of the research, and the anticipated benefits of the research substantially outweigh the risks to participants.

Exceptions to the general rule may thus be permissible in research where the foreseen benefits or risks may be greater in one or more arms, but sound scientific and ethical justification is provided in the research protocol. This imbalance should be clearly communicated to the ethics committee as well as in the informed consent procedure.

3.17 Ethical Review

All health research conducted in Zimbabwe must be reviewed by a research ethics committee and should not commence until the ethics committee has granted approval. This provides an objective appraisal of the effect of the proposed research as it affects the potential participants and the general day-to-day functioning of the health system. Section 3 of this document outlines in more detail the process of ethical review in Zimbabwe.

3.18 Distributive Justice

Research proposals should provide sufficient information to determine whether there is a reasonable likelihood that the population on whom research is to be carried out will benefit from the research and its results. Selection of participants from groups who are unlikely to be beneficiaries of subsequent applications of the research should also be justified. Research proposals should indicate whether long-term therapy would be provided to participants after the completion or termination of the study.

3.19 Research Misconduct

3.19.1 Research Misconduct Defined

Although a comprehensive statement regarding research misconduct is difficult, It has been defined as:-

> The fabrication, falsification, plagiarism or deception in proposing, carrying out or reporting results of research or deliberate, dangerous or negligent deviations from accepted practices in carrying out research. It includes failure to follow established protocols if this failure results in unreasonable risk or harm to humans, other vertebrates or the environment and facilitating of misconduct in research by collusion in, or concealment of, such action by others. It also includes intentional, unauthorised use, disclosure or removal of, or damage to, research-related property of another, including apparatus, materials, writings, data, hardware or software or any other substances or devices used in or produced by the conduct of research.
>
> It does not include honest error or honest differences in the design, execution, interpretation or judgement in evaluation research methods or results or misconduct unrelated to the research

process. Similarly it does not include poor research unless this encompasses the intention to deceive

3.19.2 MRCZ Policy on Misconduct

Any practice or conduct by a member of the research community deemed to be in breach of ethical standards for proposing, conducting and publishing research constitutes research misconduct. Violation of the national guidelines on conducting research renders the member liable to the following:-

a) The MRCZ shall bring the matter to the attention of their employer, sponsor and/or any other appropriate body. The employer/sponsor will be provided appropriate information as to the initiation, progress and conclusion of an investigation.

b) Where the person responsible has published research to which the misconduct relates, the MRCZ shall consider whether it is appropriate to inform journal editors or others of the finding.

c) If an allegation is found to have been malicious or mischievous in nature, the matter may result in disciplinary action being taken against the individual or group making the charge.

d) All allegations of research misconduct will be investigated fully, fairly and promptly.

3.19.3 Checklist of research misconduct

- refusal or failure to obtain permission to conduct research
- deception in relation to research proposals
- unethical behaviour in the conduct of research
- unauthorised use of information which was acquired confidentially
- deviation from good research practice or health and safety standards, where this results in unreasonable risk of harm to humans, other animals or the environment
- fabrication, falsification or corruption of research data
- distortion of research outcomes, by distortion or omission of data that do not fit expected results
- dishonest misinterpretation of results
- publication of data known or believed to be false or misleading
- plagiarism, or dishonest use of unacknowledged sources
- misquotation or misrepresentation of other authors
- misappropriation of the intellectual property belonging to others
- inappropriate attribution of authorship
- fraud or other abuse of research funds or research equipment
- attempting, planning or conspiring to be involved in research misconduct
- inciting others to be involved in research misconduct
- collusion in or concealment of research misconduct by others
- a material conflict of interest

4. ETHICAL REVIEW IN ZIMBABWE

4.1 The National Ethics Committee

The Medical Research Council of Zimbabwe, which houses the National Ethics Committee (NEC) was established in 1974 in terms of the Research Act of 1959 and Government Notice Number 225 of 1974 in order to, among other mandates, provide health researchers and institutions which/in which health research is conducted, with independent ethical advice and clearance on research conducted by those researchers or by/within those institutions. The MRCZ is established and supported by the Government of Zimbabwe through the Ministry of Health and Child Welfare. The MRCZ is composed of scientists, medical experts, ethicists, patient representatives, and community representatives. It is independent in its reflection, advice, and decision.

The MRCZ functions similarly to an institutional review board (internationally). The Medical Research Council of Zimbabwe undertakes the following specific tasks:

- To provide guidance, advice, and decision (in the form of 'approval /disapproval') of specific research protocols intended to be conducted in Zimbabwe by all researchers and health institutions.
- To provide ethical guidance and advice on research programmes undertaken within Zimbabwe.
- To provide ethical guidance and advice on specific ethical issues presented to it by the Institute Ethics Review Committees and any other interested parties.
- To develop and /or review, as requested, ethical guidelines for Zimbabwe.

The MRCZ is particularly concerned with research that addresses issues that are of relevance to Zimbabwe, in accordance with our specific national needs.

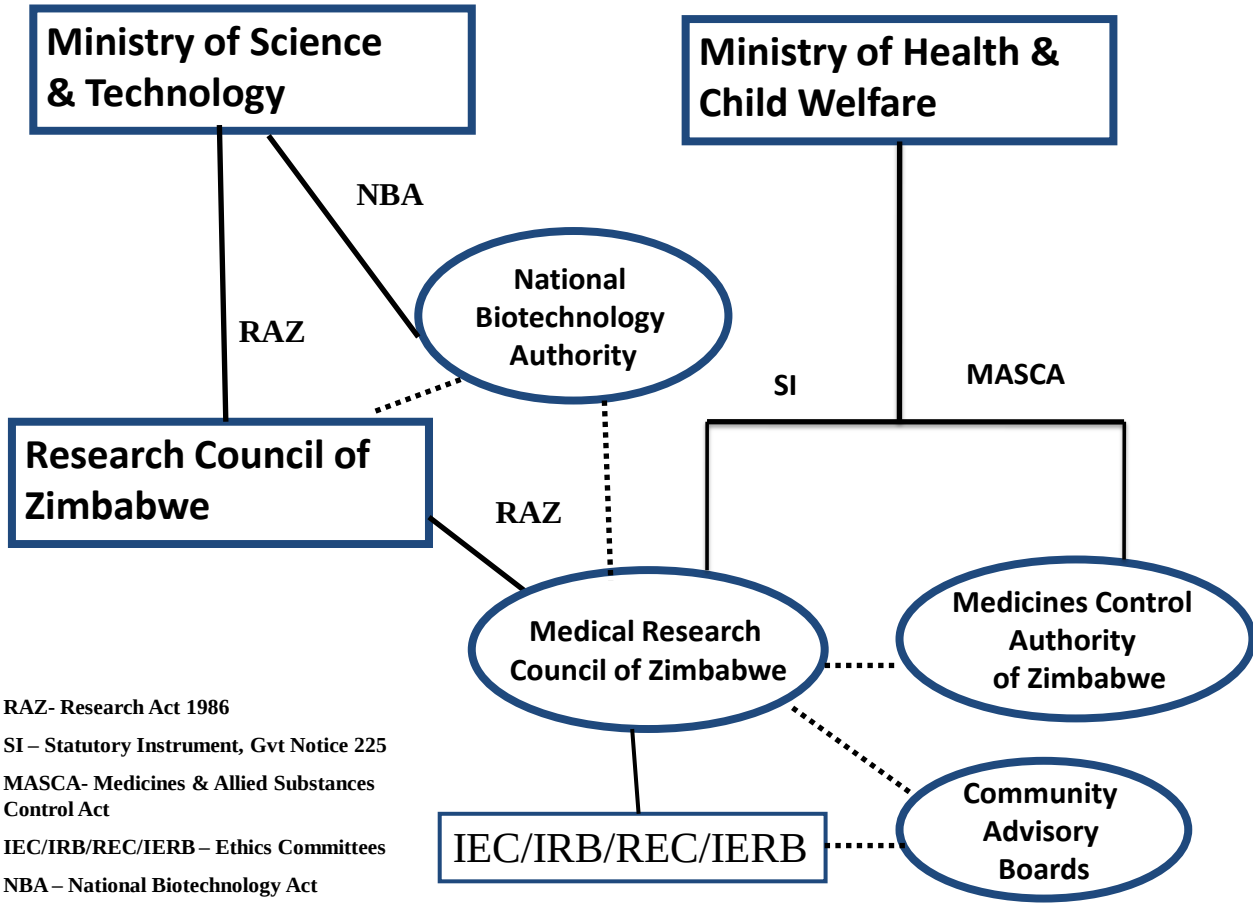
4.2 Institutional Ethics Committees

In Zimbabwe, most higher education and research institutions, and even some of the large service - rendering health institutions have ethics committees, which are mainly responsible for the institutional ethical review of research protocols. Currently the present number of research ethics committees is Four (4).

The functions of Ethics Committees include:

- Reviewing research proposals and protocols to ensure that research will be conducted in the spirit of endeavouring to promote health, and to prevent or cure disability and disease;
- Ensuring that humans involved in research are treated with dignity and that their well-being is not compromised;
- Ensuring that informed consent is obtained in the case of human participants;
- Granting institutional approval in instances where research proposals and protocols meet ethical standards;
- Monitoring all research that they would have approved.

4.3. Regulatory Framework in Zimbabwe



5. ETHICS COMMITTEES

An established research ethics committee must review and approve all research proposals involving human participants. This section details requirements for institutions in establishing an ethics committee, researchers in submitting research proposals and ethics committees in considering, reviewing and monitoring research proposals and projects.

- The primary role of a research ethics committee is to protect the rights and welfare of research participants. The primary responsibility of each member is to decide, independently, whether in his or her opinion the conduct of proposed research will protect participants.
- Institutions or organizations that undertake research involving human participants should ensure there are adequate resources to establish and maintain an ethics committee in accordance with the prescripts outlined in this document.
- Terms of reference must be set out by the institution or organization when establishing an ethics committee. Terms of reference must include the scope of its responsibilities, relationship to non-affiliated researchers, accountability, mechanisms for reporting and remuneration, if any, for members.

- The institution or organization must accept legal responsibility for the decisions and advice received from the research ethics committee and indemnify the ethics committee's members.
- Researchers without affiliation to an institution or organisation with a research ethics committee must ensure that their projects are approved by an established ethics committee.

5.1 Composition

The research ethics committee should consist of members who, collectively, have the qualifications and experience to review and evaluate the science, health aspects and ethics of the proposed research.

Research ethics committees should be independent, multi-disciplinary, multi-sectoral and pluralistic. A research ethics committee must:

- Be representative of the communities it serves and, increasingly, reflect the demographic profile of the population of Zimbabwe;
- Include members of both genders, although not more than 70% should be either male or female;
- Have at least nine members, with 60% constituting a quorum;
- Have a chairperson;
- Include at least two lay persons who have no affiliation to the institution, are not currently involved in medical or scientific research and are preferably from the community in which the research is to take place;
- Include at least one member with knowledge of, and current experience in, areas of research that are likely to be regularly considered by the ethics committee;
- Include at least one member with knowledge of, and current experience in, the professional care, counseling or treatment of people. Such a member might be, for example, a medical practitioner, psychologist, social worker or nurse;
- Include at least one member who has professional training in both qualitative and quantitative research methodologies;
- Include at least one member who is legally trained;
- The institution or organisation must ensure that the membership is equipped to address all relevant considerations arising from the categories of research likely to be submitted to it.

The research ethics committee must ensure that it is adequately informed on all aspects of a research protocol, including its scientific and statistical validity, that are relevant to deciding whether the protocol is both acceptable on ethical grounds and conforms to the principles of this document.

5.2 Appointment of Members

The institution or organisation must determine procedures for recruitment and of appointment to the research ethics committee. Members must be given formal notice of appointment and assurance that the institution or organisation will provide legal protection in respect of liabilities that may arise in the course of bona fide conduct of their duties as committee members.

5.3 Procedures

Research ethics committees should establish and record working procedures concerning:

- Frequency of meetings;
- Preparation of agenda and minutes;
- Distribution of papers prior to meetings;
- Presentation of research protocols;

- Presentation of all documents and other materials used to inform potential research participants;
- Quorum and methods of decision-making;
- Requirements for submission of research projects for ethical approval;
- Registration of applications;
- Timely review and notification of decisions;
- Written notification of decisions to researchers;
- The recording in writing of decisions made by the Committee and reasons for decisions;
- Confidentiality of the content of the protocols and of a committee's proceedings
- Reporting of adverse events;
- Reporting of amendments to protocols;
- Access to documents;
- Regular monitoring;
- Complaints procedures;
- Procedures for easy and adequate access to members of ethics committees;
- Fees charged, if any;
- End-of-trials review.

The ethics committee may approve, require amendment to, or reject a research proposal on ethical grounds. The ethics committee must record decisions in writing and should include reasons for rejection. A research ethics committee's feedback should be structured so as to be instructive to the researchers concerned. Researchers should be made aware that their statement of ethical considerations should not be a rote checklist but a real engagement with ethical issues.

In considering a research protocol, a research ethics committee may seek assistance from experts, but the committee must be satisfied that such experts have no conflicts of interest in relation to the research project under consideration.

A research ethics committee must ensure that no member of the committee adjudicates on research in which that member has any conflict of interest in relation to the research project under consideration.

A researcher must disclose to the research ethics committee the amount and sources, or potential sources, of funding for the research and must declare any affiliation or financial interest when proposing and when reporting the research.

A research proposal must include a statement of the ethical considerations involved in the proposed research. An ethics committee must be satisfied that the research protocol gives adequate consideration to participants' welfare, rights, beliefs, perceptions, customs and cultural heritage.

Researchers' proposals for health research to be conducted in community settings must include a clear plan on how the communities will be consulted or involved in the research process, and how, in general, they are to be kept informed.

Communication between research sponsors and ethics committees should be directed through the Principal Investigator. In some situations, particularly in the private sector, the Principal Investigator may be an employee of the sponsoring company or of a clinical research organisation**.** All documents and other material used to inform potential research participants should be approved by the ethics

committee, including plain-language information sheets, consent forms, questionnaires, advertisements and letters.

Research ethics committees must ensure that their members receive initial and continued education in research ethics and science, and are kept aware of current issues and developments in the broad area of ethics and science

5.4 Advocacy Role and Interpreters

An ethics committee must consider whether persons playing an advocacy role for any participant or group of participants should be invited to the ethics committee meeting to ensure informed decision-making and understanding by these participants.
Interpreters: Where research involves the participation of persons unfamiliar with the language in which the research is to be conducted, a research ethics committee must ensure that:

- The participant information statement has been translated into the participant's language;
- It is the investigator's responsibility to ensure that the participant understands the participant information statement;
- An interpreter is present during discussions with the participants about the project. As a rule the interpreter should be independent, but when the research proposal is of minimal risk, a relevant language-speaking relative or friend of the participant may be acceptable.

5.5 Expedited Reviews for Maximal Public Benefit

A research ethics committee may establish procedures for expedited review of research when this is in the public interest, and in so doing, determine the class or classes of research to which an expedited review procedure is to apply. Expedited review and approval may be considered for research where participants have a disease that may be rapidly fatal.

In general, research with potential to cause physical or psychological harm should not be considered for expedited review. This includes drug trials, research involving invasive procedures and research involving sensitive personal or cultural issues.

5.6 Recording of Decisions

A research ethics committee shall maintain a record of all research protocols received and reviewed including the:

- Name of responsible institution or organisation;
- Project identification number;
- Principal investigator;
- Title of the project;
- Date of ethical approval or non-approval;
- Approval or non-approval of changes to the protocol;
- Approval or non-approval of changes to the information sheets and informed-consent forms;
- Approval or non-approval of changes to advertising materials, letters and notices;
- Complaints from researchers whose protocols were not approved;
- The terms and conditions of approval of any protocol;
- Whether approval was by expedited review;
- Whether the opinion of another ethics committee was considered;
- Action taken by the ethics committee to monitor the conduct of the research.

For multi-centred research proposals, the ethics committee shall also record, from information provided by the investigator:

- Details of other centres involved
- The approval status of the study at each centre;
- Details of any amendments required at other centres.

An ethics committee shall retain on file a copy of each research protocol and application submitted to it for approval. The file shall include information sheets, consent forms and relevant correspondence, all in the form in which they were approved. A list shall be kept of committee members who were present during discussion of the application and when the final decision of the committee was reached.

5.7 Monitoring

A research ethics committee has the responsibility to ensure that the conduct of all research approved by the ethics committee is monitored. The frequency and type of monitoring should reflect the degree of risk to participants in the research project.
A research ethics committee must request at regular periods, at least annually, reports from the principal investigator on matters including:

- Progress to date, or outcome in the case of completed research;
- Information concerning maintenance and security of records;
- Evidence of compliance with the approved protocol;
- Evidence of compliance with any conditions of approval.

Research ethics committees should inform the principal investigator, in writing, of decisions made after the review of progress reports.
A research ethics committee may recommend and adopt any additional appropriate mechanism for monitoring, including the random inspection of research sites, data and signed consent forms, and records of interviews, with the prior consent of research participants.

As a condition of approval of each protocol, a research ethics committee shall require that researchers immediately report anything that might warrant review of ethical approval of the protocol, including:

- Serious or unexpected adverse effects on participants;
- Proposed changes in the protocol;
- Unforeseen events that might affect continued ethical acceptability of the project;
- To inform the committee, giving reasons, if the research project is discontinued before the expected date of completion.

5.8 Suspension or cessation of research

5.8.1 Researchers should inform the relevant institution/s, the review body/ies that approved the research and, wherever possible, the research participants, if the research project is to be discontinued before the expected date of completion, and why. For research at more than one site, or research where there has been multiple ethical review, it must be clearly established, before the research begins, how this information will be communicated.

5.8.2 Where the Ethics Committee finds reason to believe that continuance of a research project will compromise participants' welfare, it should immediately seek to establish whether ethical approval for the project should be withdrawn. This process should ensure that researchers and others involved in the project are treated fairly and with respect.

5.8.3 Where ethical approval for a research project is withdrawn:

a. the researcher, the institution/s and, where possible, the participants should be informed of the withdrawal;
b. the institution must see that the researcher promptly suspends the research and makes arrangements to meet the needs of participants; and
c. the research may not be resumed unless either:

1. the committee establishes that continuance will not compromise participants' welfare; or
2. the research is modified to provide sufficient protection for participants, the modification is ethically reviewed, and the modified research is approved.

5.8.4 If an institution or review body considers that urgent suspension of research is necessary before the process described in paragraph 5.8.3 is undertaken, the instruction to stop should come *via* the management of the institution.

5.9 Complaints

Ethics Committees may receive complaints about researchers or the conduct of research, or about the conduct of an Ethics Committee or other ethical review body. Complaints may be made by participants, researchers, staff of institutions, or others. All complaints should be handled promptly and sensitively.

- Each research ethics committee should establish complaints procedures for researchers and members of the public.
- Complaints should be dealt with in a confidential and ethical manner and not compromise the position of the complainant.
- Any person has the right to forward a complaint to the MRCZ, if the response of the local Ethics Committee is considered inadequate.
- The MRCZ in collaboration with Ethics Committees should develop a policy to protect whistle-blowers, these are researchers who have identified unethical behaviours on the part of colleagues and divulge such information in good faith.

6 REVIEW OF HEALTH RESEARCH IN ZIMBABWE

This Section provides details of current research review process in Zimbabwe. It also outlines the process for gaining approval to conduct a clinical trial in Zimbabwe.

As mentioned in the previous section, a research ethics committee must review all research involving human participants in Zimbabwe. When appropriate, research should be reviewed also by the following agencies and authorities:

I. Research Council of Zimbabwe

- Governed by the Research Act of 1986
- Mandate is to Promote, Direct, Supervise, and Co-ordinate all research in the country
- Control of research conducted by all bodies and persons in terms of any act
- Establishment and control of research councils and institutes
- Registration of Foreign Researchers/ Research and issuing of Bio-specimen shipment permit

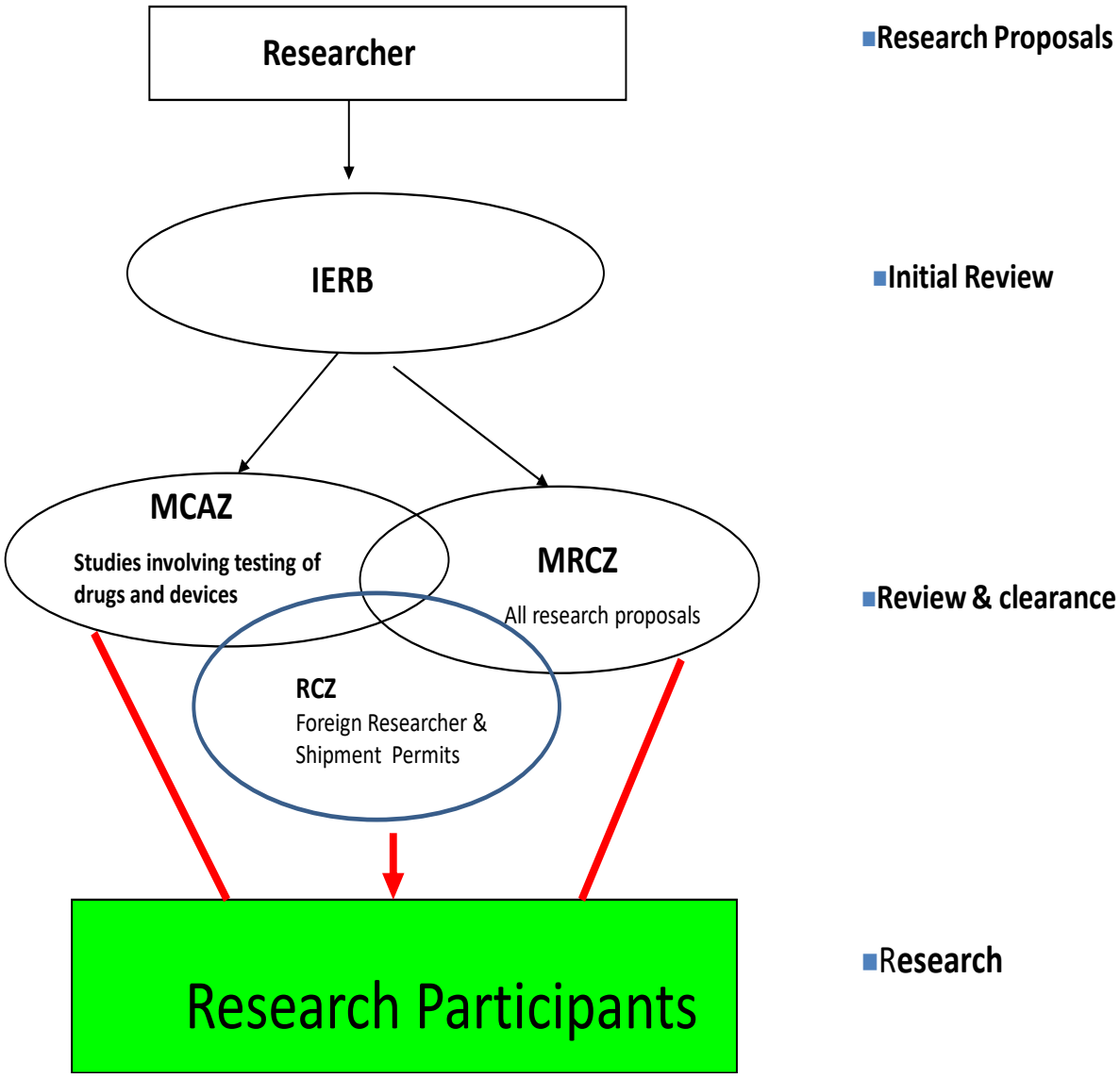
II. Medicines Control Authority of Zimbabwe

- The Medicines and Allied Substances Control Act (MASCA) of 1996
- The primary role and mandate of MCAZ is to control the manufacture and distribution of medicines and medical devices to ensure that they are safe, effective and of good quality.
- MCAZ also has the mandate to control clinical trials of medicines in humans as per MASCA sections 16-25 & sections 43-47 SI 150 of 1991
- Guidelines for Good Clinical Trial Practice in Zimbabwe (Dec04) & Guidelines for trial pharmacy procedures 2005

III. National Biotechnology Authority of Zimbabwe

- Approves all importation of GMOs in the country
- Inspects all labs that store biological agents
- Play a vital role of overseeing Bio-safety Committees
- Empowered to approve vaccine studies

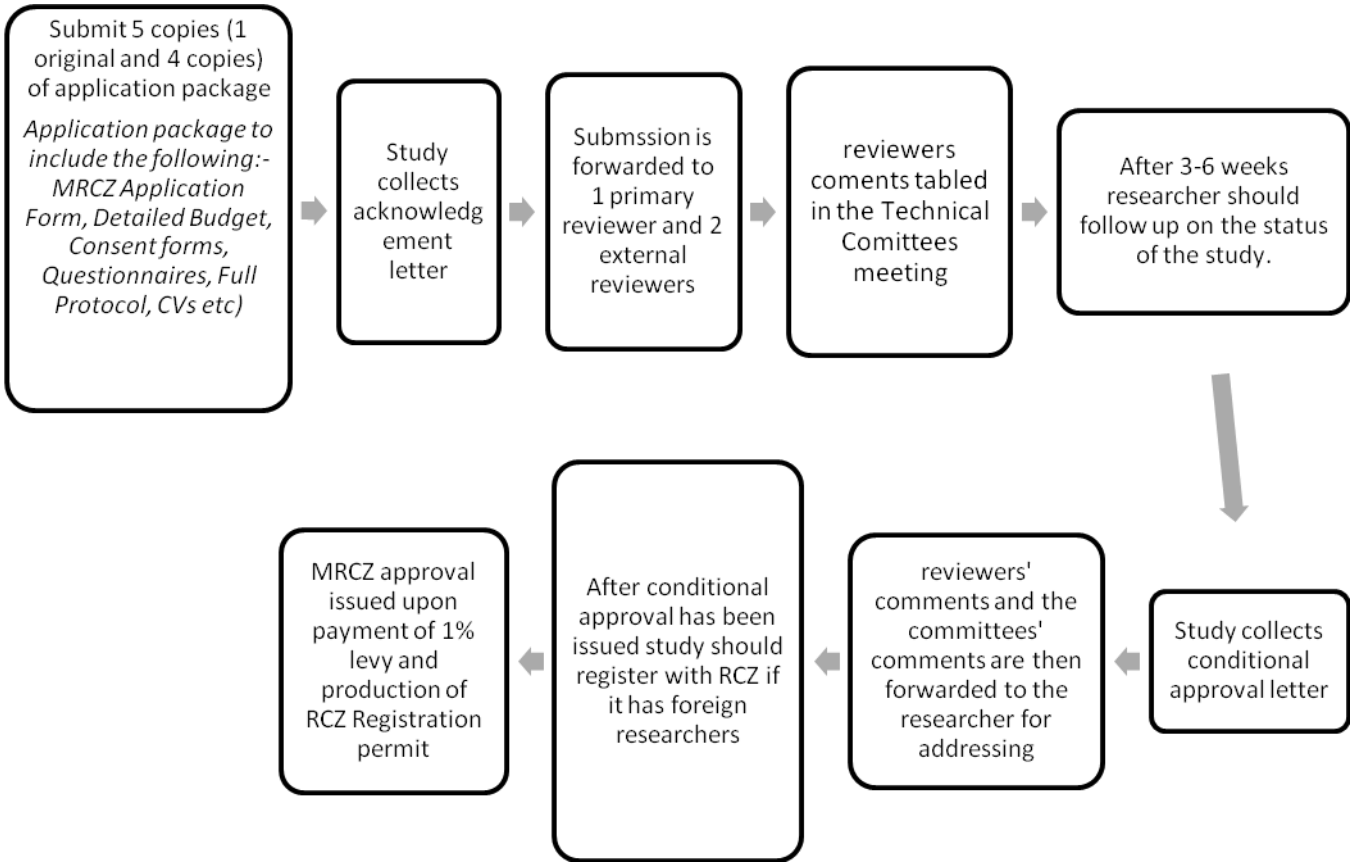
6.1 Review Processes



6.2 Submission requirements to MRCZ *(See Appendix*

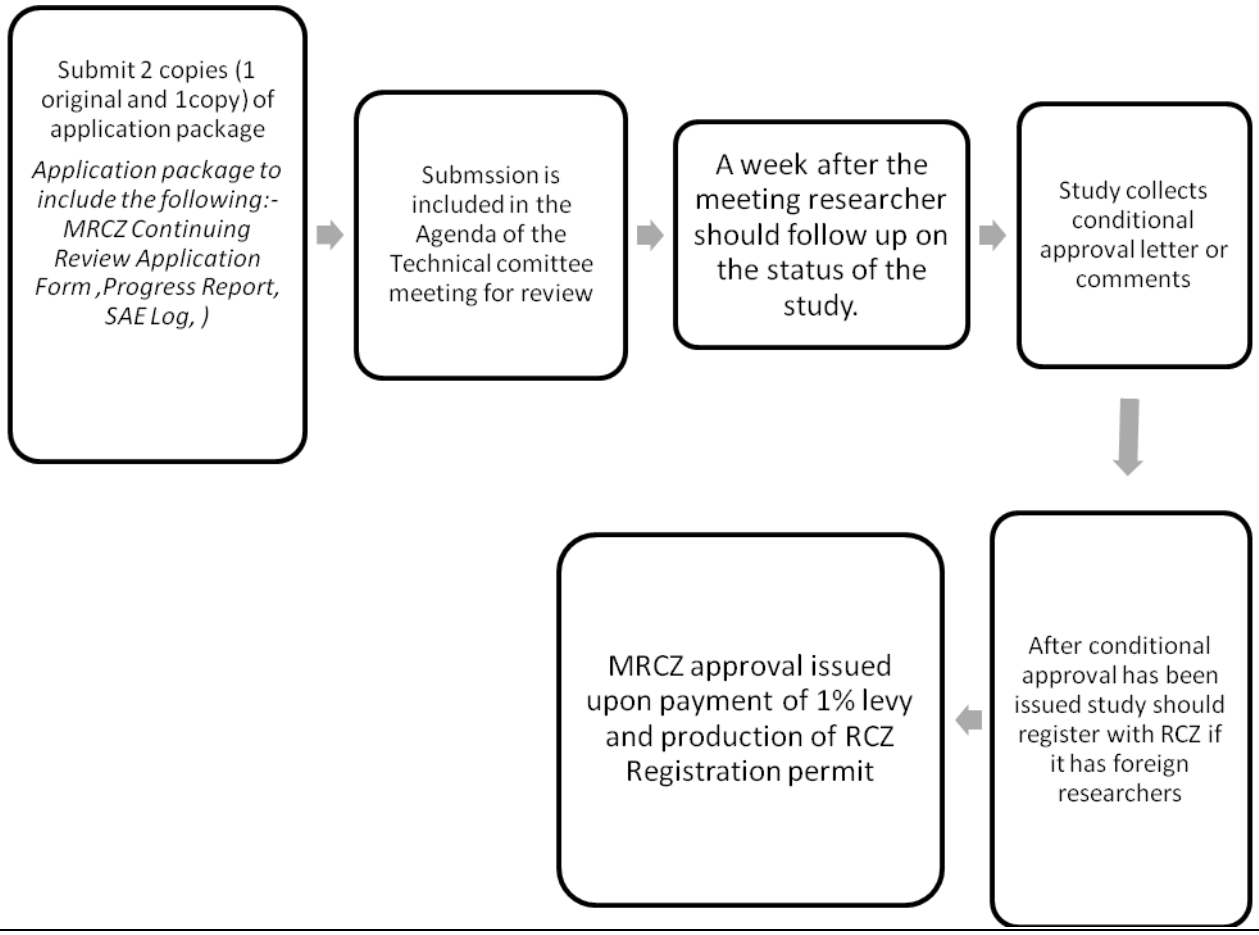
6.2.1 Initial submission

Flow Chart



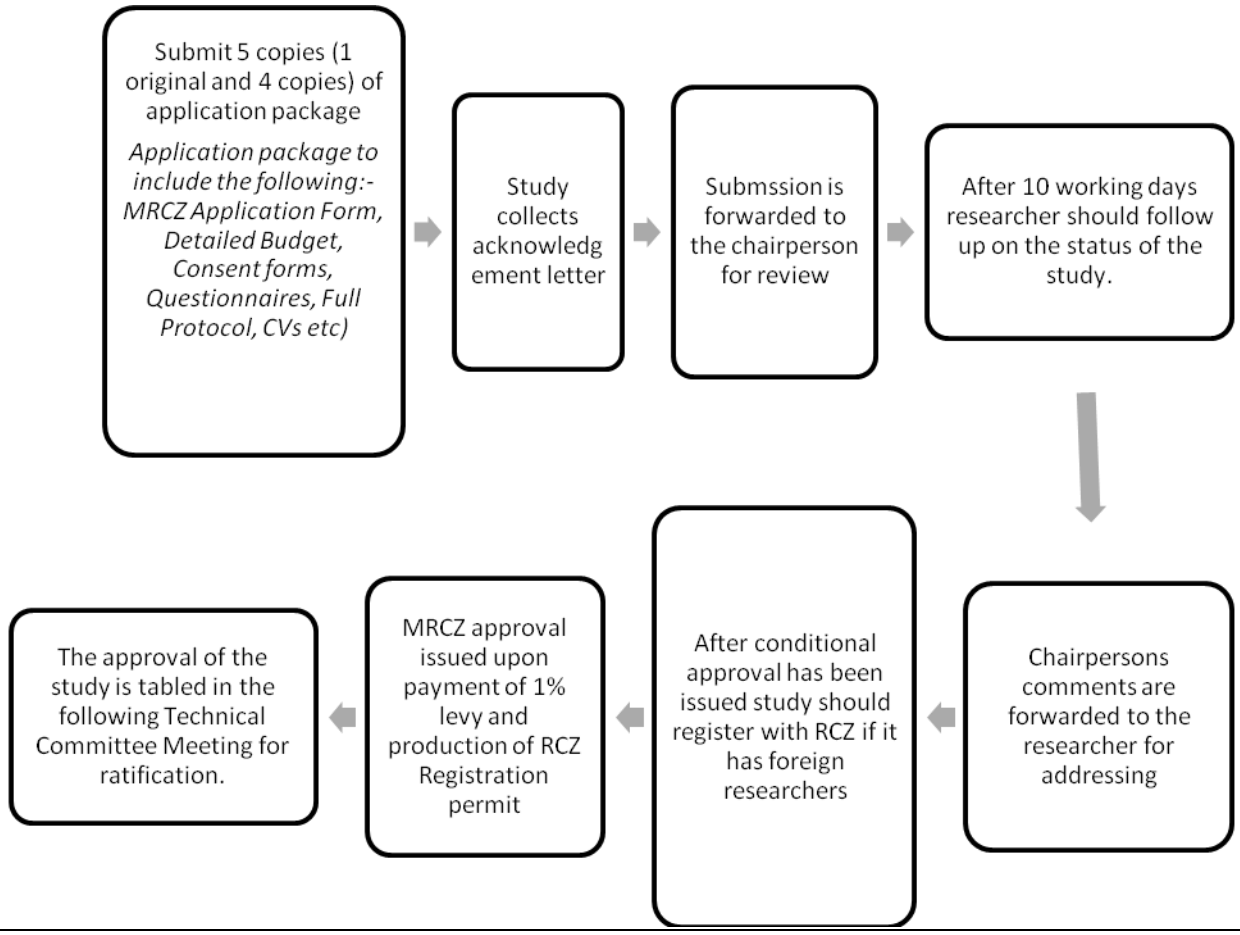
6.2.2 Continuing Review

Flow Chart



6.2.3 Expedited Review

Flow Chart



NB:- All requests for expedited review should be made in writing, stating the reason for expedited review.

6.2.4 Exempt Review

All research involving the collection of data, about living individuals through intervention or interaction with those living individuals or by collection of those individuals' private identifiable information shall be reviewed by the Ethics Committee. An Investigator is ***NOT*** empowered to make the determination of whether a research study is exempt from Ethics Committee review. The Investigator shall forward all human participant research Studies to the Ethics Committee and the Ethics Committee shall determine if the research study is exempt from review. The Chairperson or Vice-Chair makes the determination of exemption based on regulatory and institutional criteria, except as specifically noted below.

When a research study is reviewed under exempt criteria, the reviewer shall take into consideration the level of risk involved as well as ethical concerns that may pose potential harm to a participant. If the reviewer finds that the ethical issues pose more than a minimal risk to the participant but the type of research falls within the exempt criteria, the reviewer shall determine whether the study will be reviewed either as expedited or by the convened Ethics Committee.

6.3 MRCZ Levies and Fees

For MRCZ Levies and Fess see ***Appendix E***

Appendix A: THE BELMONT REPORT

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection Of Human Subjects of Biomedical and Behavioural Research, April 18, 1979

Ethical Principles and Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioural research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioural practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethic of research involving human subjects: the principles of respect for persons, beneficence and justice.

1. Respect for Persons. Respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically re-evaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to

engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense. as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to give forethought the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical. Psycho-therapeutic. and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children - even when individual research subjects are not direct beneficiaries. Research also makes is possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to

explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project; long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conflict of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied. While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal. and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the preservation of the information to the subject's capabilities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited --- for example, by conditions of immaturity or mental disability. each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails pro-providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence --- especially where possible sanctions are involved - urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favourable risk / benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons.

The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/ benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting

the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favourable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, non - arbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject - or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. --- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/ benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favour or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the

institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects. even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social. racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution. Unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions, or investigators may not be able to resolve a problem that is pervasive in their social setting. They can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

Appendix B: KEY TEXTS

The Following are international key texts that have directed the development iof these guidelines

- Nuremberg Code, 1949
- Belmont Report , 1973
- Declaration of Helsinki, October 2000

Some other useful references include:-

- ICH Guidelines For Good Clinical Practice, ICH Harmonised Tripartite Guidelines, May 1997
- International Ethical **Guidelines** for Biomedical Research Involving Human Subjects Prepared by the **Council for International Organizations of Medical Sciences** (**CIOMS**), 1991 Geneva
- International Ethical Guidelines For Biomedical Research Involving Human Participants. Council For International Organisation of Medical Sciences in collaboration with World Health Organisation (WHO). Geneva 2002
- World Health Organisation 2000. Operational Guidelines For Ethics Committees that Review Biomedical Research .Geneva. TDR/PRD/ETHICS/2000.1

Appendix C: ICH GUIDELINES FOR GCP AND DECLARATION OF HELSINKI

(*For a comprehensive document on GCP guidelines for Zimbabwe refer to www.mcaz.co.zw)*

ICH GUIDELINE FOR GOOD CLINICAL PRACTICE

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s)
2 Before a trial is initiated, foreseeable risk and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued if the anticipated benefits justify the risk.
3 The rights, safety and well being of the trial participants are the most important considerations and should prevail over interest of science and society.
4 The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trials.
5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB) / independent ethics committee (IEC) approval/ favourable opinion.
7 The medical care given to, and medical decisions made on behalf of, participants should always be the responsibility of the qualified physician or, when appropriate, of a qualified dentist.
8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9 Freely given informed consent should be obtained from every participant prior to clinical trial participant.
10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11 The confidentiality of records that could identify participants should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s)
12 Investigational product should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Appendix D: GLOSSARY

The definitions provided within this Glossary apply as they are used in the ethics and health research principles, structures and processes. These are based on the definitions in the Canadian Code of Ethical Conduct for Research Involving Humans (1996) and the ICH Guidelines for Good Clinical Practice.

Adverse Drug Reaction (ADR)
In pre-approval clinical experience with a new medicinal product or its new usages, particularly where the therapeutic dose has not been established, all noxious and unintended responses to a medicinal product should be considered as 'adverse drug reactions'. The phrase ADR indicates at least the probability of a causal relationship between a medicinal product and an adverse event. With regard to marketed medicinal products, the term applies to a drug-response that is noxious and unintended and which occurs at doses normally used in humans. (See the ICH Guideline for Clinical Safety Data
Management: Definitions and Standards for Expedited Reporting.)

Adverse Event (AE)
An adverse event may be any untoward medical occurrence in a patient or research participant who has received a pharmaceutical product that does not necessarily have a causal relationship with the treatment being researched. An adverse event (AE) may therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a medicinal product under investigation, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Anonymous Samples or Data
See De-identified samples or data

Approval (in relation to Research Ethics Committees)
The research ethics committee's affirmation that the clinical trial has been reviewed and may be conducted at the nominated institution according to the constraints set out by the ethics committee, the institution, Good Clinical Practice (GCP), and legal requirements.

Benefit
That which positively affects the interest or welfare of an individual or group, or the public generally.

Child
Subject to law in the relevant jurisdiction, a child is a minor who lacks the legal ability to make a decision whether or not to participate in research.

Clinical Trial
This is a preplanned, usually controlled, clinical study to determine the safety, efficacy or optimum dosage schedule (if appropriate) of one or more diagnostic, therapeutic, or prophylactic drugs, devices or interventions in humans selected according to predetermined criteria of eligibility.

Collectivities
Distinct human groups with common identity, their own social structures, common customs and designated leaders or other persons who represent collective interests in dealing with researchers.
Collectivities may include cultural or ethnic groups, and indigenous communities.

Competence
The ability of a person or a group to understand and make choices in accord with their own fundamental values. The term 'legal competence' indicates that a person's age and mental state satisfy certain basic legal requirements.
Confidentiality
Prevention of disclosure, other than to authorized individuals, of a sponsor's proprietary information or of a participant's identity.

Consent
The voluntary agreement of a person or group, based on adequate knowledge and understanding of relevant material, to participate in research. Informed consent is one possible result of informed choice, the other possibility is refusal.

Deception
Deception includes the withholding of essential information from research participants, deliberately misleading them about procedures and purposes, including studies in which participants are deliberately given misleading information about the purpose of a research study.

De-identified (not re-identifiable, anonymous) Samples or Data
The process of de-identification may be irreversible where the identifiers have been removed permanently or the data has been identified. These data are referred to as 'identified'. It should be recognised that the term 'de-identified' is used frequently, in documents other than this statement of the Ethics and Health Research: Principles, Structures and Processes, to refer to sets of data from which only names have been removed. Such data may remain 'potentially identifiable'.
See also Identified Samples or Data and Potentially Identifiable Samples or Data.

Ethics
A branch of moral philosophy concerned with the rational evaluation of right and wrong, justice and injustice, virtue and vice, good and bad, and related concepts and principles.

Ethical and unethical
Right or morally acceptable on one hand, wrong or morally unacceptable on the other. Conforming to the rationally acknowledged norms and standards of behaviour, or failure to conform to such norms and standards.

Ethics Committee
An independent body whose responsibility is to ensure the protection of the rights, safety and wellbeing of human participants involved in medical research (a trial). An ethics committee provides public assurance of that protection, by, reviewing and approving the trial protocol, the suitability of the investigator's facilities, and the methods and material to be used in obtaining and documenting the informed consent of the participants. Ethics committees should be independent of political, institutional, professional and market influences. The legal status of ethics committees in South Africa is established under the National Health Act, 2003 (Act No. 61 of 2003).

Families
A family is a primary social group most often consisting of parents and their offspring. However, a family may also be a group of people occupying the same dwelling place and consisting of persons who are not biologically related.

Foetus
In humans, a conceptus of seven to eight weeks' development until birth (term).

Genetic Material
Any source of DNA or RNA that can be tested to obtain genetic information. It includes cells, whether as single cells or as part of tissues, and extracted DNA and RNA.

Harm
That which adversely affects the interest or welfare of an individual or a group;
Harm extends to physical harm, discomfort, anxiety, pain, psychological disturbance and includes placing a person at social disadvantage.

Health
WHO defines health as 'a state of physical, mental and social well-being and not merely the absence of disease or infirmity'.

Human Tissue

Includes the substance, structure and texture of which the human body or any part or organ of it is composed, that is removed or separated from living human being; and includes blood, blood components and waste products.

Identified Samples or Data
Data that enables the identification of a specific individual is referred to as 'identified data'. Examples of identifiers may include the individual's name, date of birth or address. In particularly small sets of data even information such as a post code may be an identifier.
See also: De-identified Samples or Data and Potentially Identifiable Samples or Data.

Informed Consent
A process by which participants voluntarily confirm their willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to their decision to participate.
Informed consent is documented by means of a written, signed and dated informed consent form.
Informed consent is a process seeking to encapsulate a researcher's moral duty to provide sufficient information to allow potential participants to make an informed, free and rational choice whether or not to participate in a research project.

Justice
This concept concerning fairness or equity is often divided into three parts. Procedural justice is concerned with the fair methods of making decisions and settling disputes; distributive justice seeks to ensure fair distribution of benefits and burdens, while corrective justice is concerned with correcting the wrongs and harms through compensation or retribution.

Minimal Risk
This anticipates that the probability and magnitude of harm or discomfort to be experienced in the research will not be greater than those ordinarily encountered in daily life.

Monitoring
The review by a research ethics committee of ongoing research. Monitoring may take several forms, including review of annual reports, formal review of the informed consent process, establishment of a safety monitoring committee, a periodic review by a third party of the documents generated by the study, a review of reports of adverse events, and a random audit of the particular processes.

Multi-centre Research
The conduct of a research project by researchers in several autonomous institutions or organisations.
This includes multi-centre clinical trials.

Multi-centre Trial
A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Non-therapeutic
Interventions not directed to the benefit of the individual but rather towards improving scientific knowledge or technical application.

Personal Information
Personal Information is defined as information or an opinion (including information or an opinion forming part of a database), whether true or not, and whether recorded in a materials form or not, about an individual whose identity is apparent, or can reasonably be ascertained, from the information or opinion

Placebo
A product or substance known to be without effect; usually used as a control to be compared against a potentially effective substance or method that is being subjected to clinical trial.

Principal Investigator

A principal investigator is a South African-based researcher who has sole or joint responsibility for the design, conduct, analysis and reporting of the trial. The principal investigator is also responsible for the delegation of responsibilities during research.

Privacy
Privacy implies a zone of exclusivity where individuals and collectivities are free from scrutiny of others. It may also include control over the extent, timing and circumstances of sharing oneself with others, whether physically, intellectually or in terms of behaviour.

Protocol
A document that provides the background, rationale and objectives of the research and describes its design, methodology, organisation and the conditions under which it is to be performed and managed.

Qualitative Research
Qualitative research attempts to understand phenomena in entirety. It comprises research to understand social and cultural problems, and focuses on interactive processes to collect subjective information that is not structured numerically, but intuitively. Qualitative research attempts to understand human experience. It analyses thematic and narrative information. The investigator interacts with people in a sustainable manner.

Randomisation
The process of assigning trial participants to treatment or control groups, using chance to determine the assignment

Research
This involves systematic investigations to establish facts, principles and knowledge.

Research Participant
Living individual (or group of living individuals) about whom a researcher conducting research obtains data through intervention or interaction with the person or identifiable private information.

Respect for Persons
This has two fundamental aspects:
• Respect for the autonomy of those individuals who are capable of making informed choices, and respect for their capacity for self determination;
• Protection of persons with impaired or diminished autonomy, that is, those individuals who are incompetent or whose voluntariness is compromised.

Risk
The magnitude of harm and the probability of its occurrence.
See also Minimal risk

Serious Adverse Effect (event or reaction)
Any untoward medical occurrence that at any dose:
- results in death;
- is life-threatening;
- requires in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- results in a congenital anomaly or birth defect.

Sponsor
An individual, company, institution or organisation that assumes financial responsibility for all or part of a particular research study or clinical trial.

Therapeutic
Descriptive of interventions directed to the wellbeing of the individual or community involved.

Vulnerable Participants

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable participants include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Well-being (of the trial participants)
The physical and mental integrity of the participants participating in a clinical trial

Appendix E: MRCZ LEVIES AND FEES

ITEM	AMOUNT
1. Normal Registration Fee (New Studies)	**$500**
2. Fast Track Review Fee (New Studies)	**$1 000 per study**
3. Penalty for late submission of Annual Continuing Application	**$200 after 30 days**
	$1 200 exceeding 6 months
4. Application for study extension	**$100 per study**
5. Levies	**1% of Total Budget**
6. Inspection Fee	**$300**
	(Only applicable to cause inspections or upon request)
7. Amendment Fee	**$50 per Amendment**
8. Fast Track of Amendment Fee	**$100 per Amendment**
9. Training Fee	**$20 per head per day**
10. Penalty for Late Submission of SAE / AE	**$20 per day**

Appendix F:- GOVERNMENT NOTICE 225 OF 1974