

GUIDELINES FOR GOOD PRACTICE IN THE CONDUCT OF CLINICAL TRIALS IN HUMAN PARTICIPANTS IN SOUTH AFRICA

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PREAMBLE

This is the first edition of the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa. The Guidelines are produced as a reference text for researchers, research sponsors, the general public and all those who have an interest in clinical trials research in South Africa. They provide guidance on minimum standards that are acceptable for conducting clinical trials in South Africa.

These guidelines have been compiled by a working group convened by the Director General of the Department of Health and has principally included representatives from the Department of Health, South African Drug Action Programme / World Health Organisation, Medical Research Council, the Medicines Control Council, Universities of Natal and the Witwatersrand and the AIDS Law Project. It has been compiled over a period of a year during which close interaction with major players in the South African research community has been critical.

The purpose of these guidelines is to provide South Africa with clearly articulated standards of good clinical practice in research that are also relevant to local realities and contexts.

These guidelines are closely related to the regulatory requirements of the Medicines Control Council and those of the National Department of Health's legislative and regulatory framework. It is therefore critical that these guidelines are used by research ethics committees, researchers, trial participants, principal

investigators of trials and sponsors alike so as to ensure a standardised and ethical approach to clinical trial activities in South Africa. The guidelines are applicable to both academic and contract clinical research.

The document is not exhaustive. It does however provide references of national and international texts to guide the reader to particular areas of interest. The document is unique in that it provides the first attempt at addressing issues related to clinical trial research in developing countries.

I believe these guidelines would contribute significantly to ensuring good health and promoting the health of South African citizens.

Dr ME Tshabalala-Msimang
Minister of Health

Date: 14 - 09 - 2000

ACKNOWLEDGEMENTS

The national guidelines have been developed to promote good practice and standards in the conduct of clinical trials in South Africa.

The process to develop these guidelines started in 1998 with the formation of a representative expert- writing group which by the end of 1998 had produced a conceptual framework. Subsequently, the process was taken forward by a small task team which has produced the final document.

The drafting team relied on their experiences and knowledge, experts' advice, available literature, various country experiences and a variety of internationally accepted standards and guidelines. I hereby thank all those who granted us permission to refer to their documents.

I would like to express my sincere gratitude to all those who contributed to the drafting and writing of these guidelines. Thanks to the South African Drug Action Programme/World Health Organisation; Medicines Control Council; Medical Research Council; Universities of Natal and Witwatersrand; Lawyers for Human Rights; Directorate: Health Systems Research, Research Co-ordination and Epidemiology and Directorate: Pharmaceutical Services.

I would also like to sincerely thank all persons and groups that reviewed and made constructive comments and inputs to the guidelines including South African Institute for Medical Research; South African Pharmaceutical Clinical Research Association; Quintiles Clindepharm; MEDUNSA; Medical Research Council; Universities of Cape Town; Free State and Pretoria; Technikon Pretoria; ML Sultan Technikon; Technikon Witwatersrand; Indian Ocean Triangle Quinteles; WHO/EURO Programme for Pharmaceuticals; Health Professions Council of South Africa; Clinical Quality Concepts; WHO Collaborating Centre for Drug Policy; Rand Afrikaans University, SmithKline Beecham (Southern African Region) and all other contributors

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1. INTRODUCTION

The value of clinical trials as the optimum methodology for the testing and evaluation of new treatments and medicines is well recognised within the South African research community. South Africa provides a particularly unique research environment encompassing high technological medical expertise and infrastructure and a significant burden of disease. The racial - cultural diversity provides an opportunity to investigate racially specific disease traits, whilst the shift from rural to urban areas provides a wealth of patients to investigate emerging and re-emerging diseases lit up by urban deprivation.

Risk inherent in this is the potential for unscrupulous, unethical and unnecessary conduct of clinical research. This is more likely to happen in poor populations with low levels of literacy, an unquestioning acceptance of authority and a need for health services of all descriptions. Currently it is estimated that the clinical trial industry in South Africa has grown by as much as 40% from 1997-1998 (Christley 1998) and yielded an estimated total budget of R826 million during 2000 (Joffe, 2000). In the light of this growth the need to carefully regulate and guide the conduct of clinical trials becomes urgent and necessary.

1.1 WHY GUIDELINES?

In recognition of this necessity a working group convened by the Director General of Health developed the first edition of the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa. The purpose of these guidelines is to ensure that clinical trials conducted on human participants are designed and conducted according to sound scientific and ethical standards within the framework of good clinical practice. Compliance with these standards provides the public with assurance that the rights, safety and well being of trial participants are protected and that the clinical trial data are credible.

1.2 PRINCIPLES

These guidelines should be read in the context of the Declaration of Helsinki, October 2000 and the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, May 1997 (Appendix A).

Although well designed clinical trials will undoubtedly fit in within these modern ethical sentiments, the potential to violate the rights of trial participants particularly in vulnerable communities necessitates the need to articulate ethical guidelines for clinical trials.

These include the following:

- Respect for persons
- Beneficence and non maleficence
- Justice

The practical application of these principles requires research studies to have distinct components built into them. These include relevant and appropriate study rationale, optimal study design, investigator competence, a balance of risks and benefits for participants, transparency, patient privacy, ethical review and impartial oversight of consent procedures. To follow is a brief discussion on some of these issues as they relate to South Africa.

A. Study Rationale and Motivation

A study rationale and motivation which does not ask relevant and important questions is unethical.¹ Whilst maintaining the highest standards of clinical research it is important that clinical trials are based on priority, country specific research questions. Relevant and important questions should also be problems that significantly affect local and regional population. Study rationale should demonstrate that the study question has not been substantially answered and that adequate systematic review of the subject under discussion was done. The findings of which must be translatable into mechanisms for improving the health status of South Africans. Solutions should have the potential for implementation.

B. Study Designs

Appropriate designs are critical in contributing to answering scientific questions. The design must therefore demonstrate a high probability for providing answers to specific research questions. Adequate supporting information and explanation on the study sample size and study population must also be provided. A study on a population comprising a vulnerable group must be able to justify the choice of that population on scientific and social justice grounds. The researchers should be able to say why they have chosen that vulnerable group rather than the other and if a population that is a vulnerable group will stand to benefit in ways that reduce their vulnerability. The design of the drug trial should in no way prejudice the ongoing treatment and care of patients, nor should it anyway undermine or confuse patients with respect to the best available local standard treatment practices and national policy approaches.² If these are not ensured, then the design is unethical.

C. Investigator Competence

The investigator's competence is assessed by two major parameters: Technical and humanistic. Technical competence which includes research competence is assessed by education, knowledge, certification and experience. Humanistic parameters require compassion and empathy. This is provided by a proper clinical and research environment, encompassing good research mentoring. In all cases the Principal Investigator must be a South Africa based scientist (resident in South Africa).

D. Balance of Harm and Benefit

A risk benefit analysis of the study should precede the conduct of the research itself. Risk-benefit analysis should take full cognisance of benefits and harms beyond the life of the study itself, particularly in the case of chronic life threatening conditions. Alternative ways of providing benefits to the patients might be available without research; thus the distinction between the probability of harm and the possible benefits of the effects must be made. The principal investigator has the ethical duty of excluding participants who are at undue risks.

E. Transparency

Once the trial has obtained approval, trial information is placed on a central register. The following data items on the trial are recorded in this register: The research question, information on the principal investigator, location of the trial, date of when approval was given, outcomes of the trial, including a summary report, date when trial was commenced/completed and where appropriate, information concerning the premature termination of the trial, the size of funding for trial research and the investment of industry in different aspects of biomedical intervention. The database will serve to promote transparency, good co-ordination and systematic review to prevent unnecessary trials.

F. Privacy

The participants right to privacy must be protected at all costs. This is maintained via the use of appropriate precautions regarding subject identifiers. This will also include electronic / computerised records and access thereof of such information.

G. Ethical Review

This provides an objective appraisal of the research proposal as it affects the potential participants and the general day to day functioning of the health system. Three methods are currently used. (I) Ethics Committees, which are usually made up of lawyers, medical practitioners, bio-ethicists and community representatives, are by far the commonest; (II) Data and safety monitoring committees. These committees oversee ongoing clinical trials with respect to treatment, efficacy and safety. In the advent of clear evidence of efficacy or harm, prior to the end of the trial, premature termination can be recommended on ethical grounds; and (III) The Regulatory Authority (i.e. the Medicines Control Council) which is responsible for reviewing the study design, and in so doing review all significant ethical questions.

H. Informed Consent

Informed consent is a necessary but not sufficient requirement for ethical conduct. Obtaining informed consent implies the provision of information to potential participants regarding the nature of the research procedure, scientific purpose and alternatives to study participation. Participants' comprehension is addressed by laying out this information in a clear and simple style. In South Africa, this must be achieved via the use of culturally acceptable practices including the use of the participant's language. The conditions under which the consent is granted must be free of coercion, undue influence or incentives. Treatment for a given condition, which might be an attribute of the clinical trial design should not be denied by the refusal to participate. Withdrawal from the clinical trial at any time will not result in undue clinical penalties to the participant.

I. Safety Monitoring

Safety monitoring of participants during and for defined periods after a clinical trial is an ethical requirement. This involves the prompt reporting of serious adverse events and the appropriate management of such an event.

J. Multi-centre Studies

The number of multi-centred clinical trials being undertaken in South Africa has increased dramatically in recent years. There is a need to ensure that designs are appropriate for the local setting and that particular modifications are made to the local study when required e.g. inclusion / exclusion criteria. It is unacceptable for developed country participants to have better standards of care offered in the study when compared to South African participants. When South Africa is chosen for a clinical trial while the trial is not undertaken in the country of origin an explanation should be sought about 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 the appropriateness of incentives packages to trial participants and remuneration packages for investigators.

1.3 SCOPE OF THESE GUIDELINES

These guidelines focus on the management and regulation of drug trials on human participants. These guidelines have not specifically addressed clinical trials on complementary medicines, traditional medicines, non-pharmacological interventions including surgical procedures, medical devices and X-rays. However, these guidelines are such that, in the absence of alternatives, the basic principles outlined in this document may be used to guide any research involving human participants. These guidelines have been guided by and based extensively on the following documents:

- Declaration of Helsinki, October 2000
- International Guidelines for Ethical Review of Epidemiological Studies, Council for International Organisations of Medical Sciences (CIOMS), 1991
- World Health Organisation, WHO Technical Report Series, No. 850, Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995

- World Health Organisation (2000) Operational Guidelines for Ethics Committees That Review Biomedical Research. Geneva. TDR/PRD/Ethics/2000.1
- MEDSAFE, New Zealand Regulatory Guidelines for Medicines, Volume 3: Interim Good Clinical Research Practice Guideline, August 1998
- ICH Guideline for Good Clinical Practice, ICH Harmonised Tripartite Guideline, May 1997³
- Association of the British Pharmaceutical Industry Clinical Trial Compensation Guidelines, Issued January 1991, Reprinted March 1994
- Institutional Review Board (IRB) Guidebook. Office for the Protection from Research Risks – National Institute of Health, USA, 1993

In the event that these Guidelines differ from any of the above texts, these Guidelines will apply. The responsibility for deviation with any of the above documents lies with the authors of these Guidelines.

1.4 GUIDELINES AND LEGISLATION

These guidelines will be enforced by regulations. In addition, clinical trials to be conducted in South Africa are also required to obtain ethics approval through an approved ethics committee. A process to register clinical trials will be established. Compliance with these guidelines is compulsory under the direction of the Director General of Health. In the event that both a legal requirement and the guideline applies to a particular issue or activity of the clinical trial, the legal requirement will always apply.

1.5 ROLES AND RESPONSIBILITIES

This document outlines the roles and responsibilities of the various parties involved in clinical trials in South Africa. Specifically, these include:

1.5.1 The Regulatory Authority (MCC):

All clinical trials of both non-registered medicinal substances and new indications of registered medicinal substances must be reviewed by the Medicines Control Council (MCC). The MCC has a statutory obligation to ensure that the drugs available in the country fulfil the necessary requirements for safety, quality and efficacy. In the case of an ongoing trial where there are serious breaches of Good Clinical Practice, the MCC can close a trial down. Reference to the regulatory authority in this document refers to the MCC.

1.5.2 Department of Health

All clinical trials to be conducted in South Africa will be required to register and will be issued a study number by the Department of Health through National Health Research Ethics Council. Section 1.6 refers.

1.5.3 The National Health Research Ethics Council:

This body will have the overall responsibility to promote, ensure and monitor compliance by approved ethics committees in South Africa with relevant legislation, regulations and guidelines including Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa. It plays an important role in the issuing study numbers of clinical trials in South Africa and is expected to be established under the National Health Bill. This body reports directly to the Minister of Health and is provided with secretariat support from the Directorate Health Systems Research, Research Co-ordination and Epidemiology (HSRRCE).

1.5.4 Ethics Committees:

The main responsibility of ethics committees in South Africa is to ensure the

protection and respect of the rights, safety and well being of participants involved in a trial and to provide public assurance of that protection by reviewing, approving and providing comment on clinical trial protocols, the suitability of investigator(s), facilities, methods and procedures used to obtain informed consent. In the execution of these responsibilities committees should be guided by relevant South African ethical guidelines, professional standards and codes of practice. The performance of ethics committees should be systematically audited in a structured way.

1.5.5 The Principal Investigator:

The principal investigator is a South Africa based scientist who has a sole or joint responsibility for the design, conduct, delegation of trial responsibilities, analysis and reporting of the trial. The principal investigator is accountable to the sponsor and regulatory authorities as required by these Guidelines. The PI should be knowledgeable and have an understanding of the drug, its toxicology and safety. In the case of a multi-centred trial there must be a local principal investigator (PI) attached to each site. It is unacceptable to have an "absentee" PI who is based in another country.

1.5.6 The Sponsor:

An individual, company, institution, or organisation which takes responsibility for the initiation, management, and / or financing of a clinical trial.

1.5.7 The Monitor:

The monitor is appointed by and reports to the sponsor. The monitor is responsible for overseeing the progress of a clinical trial and ensuring that it is conducted, recorded and reported in accordance with protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), Good Laboratory Practice (GLP), Good Pharmacy Practice (GPP), these guidelines and other applicable legislation and regulations.

1.5.8 The Auditor:

The auditors are independent individuals appointed by sponsors to conduct a systematic and in-depth examination of trial conduct and compliance with the protocol, SOPs, GCP, GLP, GPP and the applicable regulatory requirements. An audit is separate from routine monitoring or quality control functions. The regulatory authority may also appoint an auditor to a trial.

1.5.9 The Inspector:

The inspector is a suitably qualified employee of the MCC whose responsibility is to conduct announced or unannounced inspection visits at clinical trial sites as required/instructed by the MCC. Most inspectorate visits will be prearranged but some will not especially where there is suspected serious breaches of the GCP or malpractices.

1.6 PROCESS FOR A CLINICAL TRIAL APPROVAL IN SOUTH AFRICA

The following two steps are required as a standard approval process in South Africa:

- MCC Approval - PI / Sponsor apply for approval to conduct a Trial of Non-registered drug or registered drug for new indications; and
- Ethics Committee Approval – ethical approval for all clinical trials

In addition a system to ensure monitoring of all research will be set up through the National Health Research Ethics Council and local ethics committees which will involve each study being registered and issued with a study number. A document will be made available for this

registration process during 2001.

Footnotes Chapter 1

[1] Researchers can seek guidance from the Essential National Health Research (ENHR) committee on relevant and important questions for South Africa. For further information on the ENHR committee please contact the Minister of Health, c/o Health Systems Research, Research Co-ordination and Epidemiology Private Bag X828, Pretoria, 0001

[2] Where trials are in contradiction to standard national policy and treatment practices, a motivational statement within the protocol as to why this is the case is required. e.g. testing new vaccines which may disrupt current EPI schedules

[3] Written permission to use the ICH guidelines on a non-commercial basis was given by the ICH secretariat.

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2. PROTECTION OF STUDY PARTICIPANTS

2.1 GUIDING DOCUMENTS

The welfare and personal integrity of the participants is the responsibility of the principal investigator. The principal investigator must follow fully the guidelines set out in the Declaration of Helsinki, ICH Guidelines for Good Clinical Practice (Appendix A) and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS 1993).

2.2 ETHICAL REVIEW

All medical research involving human participants must undergo an independent ethical review. An autonomous accredited ethics committee must ascertain that the protection of the participant is assured in the evaluation of clinical trial applications.

In the evaluation of clinical trials protocols or study applications, these bodies must ensure the protection of participants in accordance with international standards and guidelines.

An ethics committee should consider the following issues when reviewing a proposal for a clinical study:

- the scientific relevance of the clinical study;
- the suitability of the investigator(s) for the proposed study in terms of his/her availability, qualifications, experience, supporting staff, and available facilities;
- the relevance of the study rationale and the appropriateness of the inclusion / exclusion criteria to the South African context;
- the suitability of the study application in relation to the objectives of the study; i.e. the potential for reaching sound conclusions with the smallest possible exposure to risk of participants, and the justification of predictable risks and inconveniences weighed against the anticipated benefits for the participants and/or others;
- the suitability of study population, whether they constitute a vulnerable group, if so whether justified and whether sufficient measures to protect their interest are in place;
- that the number of participants to be recruited is adequate to demonstrate the predicted effect;
- the risk-benefit analysis take full cognisance of benefits and harms beyond the life of the study itself, particularly in relation to chronic life-threatening conditions;
- if placebos are to be used, whether their use can be justified;
- that by their participation in a clinical study the participants or other persons in the establishment or clinical centre are not denied timely access to medical personnel, investigations, equipment or procedures;
- the means by which initial recruitment is to be conducted and by which full information is to be given and informed consent is to be obtained. All written information for the participant and/or legal representative must be submitted in its final form;
- the adequacy and completeness of the written information to be given to the participants, their relatives, guardians and, if necessary, legal representatives;
- that the application allows the participants and/or their representatives adequate time to consider the patient information package before informed consent is sought;
- the content of any advertisements or public notices which will be used to recruit participants to a study;
- that the study protects participants' rights to privacy;
- the provision of compensation/treatment in the case of injury or death of a participant if attributable to a clinical study, and the insurance or indemnity to cover the liability of the investigator and sponsor;
- the extent to which investigator(s) and participants are to be compensated for participation;
- making specific recommendations regarding the continuation of treatments beyond the life of the study, or mechanisms to ensure that participants are fairly protected;
- the demographic information available to assess whether the patient population is adequate to support the study;
- whether there is any cost to the participant and no charges to medical aids or insurance for protocol specific procedures;
- whether the product will be made available to participants after the study ends, and if so whether there is any cost to the participant to continue treatment;
- whether any restrictions will be placed on the publication of results; (i.e. ensure there is a written commitment from investigators to publish the results of trials and there is no contractual clause which reserves the right of publication to the sponsor only);
- the adequacy of the statistical methods proposed to evaluate the data generated; and
- whether the study is advancing the body of knowledge on the subject.

2.3 SPECIAL CLASSES OF PARTICIPANTS

South African ethics committees must give special consideration to protecting the welfare of special classes of participants, such as children and adolescents, pregnant women, prisoners, people with mental disabilities, people for whom English is not a first language or people from vulnerable communities. The following are guidelines for the inclusion of such populations in a clinical trial.⁴

2.3.1 Children and Adolescents

Research in children should only be approved if:

- The research does not place the child / minor at no greater than minimal risk.
- The research involves more than minimal risk but provides direct benefit for the child / minor. The risk must however be justified by the potential benefit.
- The research involves greater than minimal risk, with no prospect of direct benefit to the child / adolescent but there is a high probability that it will provide "generalisable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition" (IRB, 1996:11). In addition the risks must represent only a minor increase over minimal risk and the intervention or procedure "presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or education settings" (IRB, 1996:11).
- In all cases, assent from both child and permission from their parents or legal guardians must be sought. No other caregiver can provide consent on behalf of a child to participate.
- Child Assent:⁵ The Ethics committee must ensure that adequate steps are outlined in the protocol to obtain the child's assent, when in the judgement of the Ethics Committee the child is capable of providing such assent. When the Ethics Committee decides that assent is required, it must also state if and how assent must be documented.
- Parental Permission: Where the research does not involve greater than minimal risk to the child, or involves greater than minimal risk but presents a likely direct benefit to the child, the Ethics Committee may find that the permission of one parent is sufficient. Permission from both parents is necessary where the research involves greater than minimal risk, no direct benefit to the child but is likely to produce generalisable knowledge about the subject's condition. "Exceptions would include: 1) one parent is deceased, unknown, incompetent, or not reasonably available, or 2) when one parent has legal responsibility of the care and custody of the child". (IRB Policy and Procedure Manual 1997:4).

2.3.2 Women and pregnancy

Ethics Committees must give extra attention to research that involves women who are or may become pregnant, because of the additional health concerns of mothers during pregnancy and the need to avoid unnecessary risk to the foetus. Reasons for excluding women from trials should be adequately justified both from the point of view of protecting the health of a foetus and from the perspective of whether such exclusion is scientifically supportable. The IRB: Policy and Procedure Manual (1997) states that "No research activities involving pregnant women and foetuses may be undertaken unless:

- Appropriate studies on animals and non pregnant individuals have been completed;

- The purpose of the activity is to meet the health needs of the mother of the particular foetus, the risk to the foetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity;
- Individuals engaged in the activity will have no part in 1) any decision as to the timing, method and procedures used to terminate the pregnancy, and 2) determining the viability of the foetus at the termination of the pregnancy; and
- No procedural changes which may cause greater than minimal risk to the foetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

2.3.3 Pregnant Women as Participants⁶

No pregnant woman may be involved as a subject in any research activity unless

- the purpose of the activity is to meet the health needs of the mother and the foetus will be placed at risk only to the minimum extent necessary to meet such needs, or
- the risk to the foetus is minimal.

Any activity permitted above may be conducted only if the mother is legally competent and have given informed consent after having been fully informed regarding possible impact on the foetus. The father's informed consent need not be secured if

- the purpose of the activity is to meet the health needs of the mother;
- his identity or whereabouts cannot reasonably be ascertained;
- he is not reasonably available; or
- the pregnancy resulted from rape.

2.3.4 Foetuses in utero as Participants

No foetus in utero may be involved as a subject in any research activity unless

- the purpose of the activity is to meet the health needs of the particular foetus and the foetus will be placed at risk only to the minimum extent necessary to meet such needs, or
- the risk to the foetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

Any activity permitted above may be conducted only if the mother and father are legally competent and have given their informed consent. The father's informed consent need not be secured if

- his identity or whereabouts cannot reasonably be ascertained;
- he is not reasonably available; or
- the pregnancy resulted from rape.

2.3.5 Foetuses ex utero, Including Nonviable Foetuses, as Participants

Until it has been ascertained whether or not a foetus ex utero is

viable, a foetus ex utero may not be involved as a subject in any research activity unless

- there will be no added risk to the foetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or
- the purpose of the activity is to enhance the possibility of survival of the particular foetus to the point of viability.

No nonviable foetus may be involved as a subject in any research activity unless

- vital functions of the foetus will not be artificially maintained;
- experimental activities which of themselves would terminate the heartbeat or respiration of the foetus will not be employed; and
- the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

Any activity permitted above may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if

- his identity or whereabouts cannot reasonably be ascertained;
- he is not reasonably available; or
- the pregnancy resulted from rape.

2.3.6 Prisoners

Ethical review must take cognisance of the impact of a prisoner's incarceration on their ability to make a truly voluntary and uncoerced decision whether or not to participate as participants in research.

In addition, when reviewing research involving prisoners, ethics committees must meet the following specific requirements:

- A majority of the ethics committee (exclusive of prison members) shall have no association with the prison(s) involved, apart from their membership on the ethics committee; and
- At least one member of the ethics committee shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one ethics committee only one ethics committee need satisfy this requirement.

The following clinical trials involving prisoners is permitted:

Clinical trials conducted or supported in South Africa may involve prisoners as participants only if 1) the research has been registered with the National Health Research Ethics Council, and 2) and in the judgement of the MCC and the relevant approved ethics committee, the clinical trial involves the following:

- study of the possible causes, effects, and processes of incarceration, and of criminal behaviour, provided that the

study presents no more than minimal risk and no more than inconvenience to the participants;

- study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;
- research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) only after appropriate experts have been consulted; or
- research on practices, both innovative and accepted, that have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the Ethics Committee to control groups that may not benefit from the research, the research may proceed only after appropriate experts have been consulted.

2.3.7 People with Mental Disabilities or Substance Abuse Related Disorders

People with mental disabilities include: those people with psychiatric, cognitive or developmental disorders. The issue with these groupings of people when it comes to research is their capacity for reason regarding participation and comprehend information provided. This issue is also applicable to research on persons with substance abuse related disorders. Institutionalisation may also further compromise a person's ability to make a truly voluntary decision to participate in a study.

Research in people with cognitive disabilities or with substance abuse related disorders must therefore:

- Be relevant to mental disabilities or substance abuse related disorders so that it is necessary to involve people who are mentally disabled or with substance abuse related disorders.
- Provide sufficient justification for involving people with mental disabilities or substance abuse related disorders who are institutionalised as the study population.
- Ensure appropriate evaluation procedures for ascertaining participants' ability to give informed consent. If participants are deemed unable to understand and to make a choice, then an appropriate individual, able to consent on their behalf must be sought.
- Ensure that consent is free from coercion and risk to patients.
- Ensure that no more than minimal risk is involved, or if minimal risk is involved, the risk is outweighed by the anticipated benefits of the study for the participants and the importance of the knowledge which will emanate from the research.

2.3.8 Vulnerable Communities

South Africa is home to a number of vulnerable communities.⁷ Particular caution must be practised before undertaking research involving participants in such communities and ethics committees must ensure the following:

- persons in these communities will not ordinarily be involved in research that could be carried out in populations from developed communities.
- the research is responsive to the health needs and the priorities of the community in which it is carried out.
- research participants should know that they are taking part in research and this research should only be carried out with their consent. This implies that particular attention is paid to the content, languages and procedures used to obtain informed consent.
- the research protocol should not adversely affect the routine treatment of patients, nor disrupt routine management protocols.

2.3.9 Other Special Groups

The discussion on special groups should not be limited to those already mentioned. Other special groups include: Traumatized and comatose patients, terminally ill patients, elderly or aged patients, minorities, students, and employees. Ethics committees must ensure special consideration is given to all these groups, particularly around informed consent. For a more detailed discussion on informed consent please refer to the section 3.5 of this document.

Footnotes Chapter 2

[4] For further, more detailed discussion on special classes of participants refer to Chapter 5, Institutional Review Board (IRB) Guidebook, 1993, NIH, USA, <http://www.nih.gov/grants/oprr/irb/>

[5] Worth noting is the following discussion provided by the IRB Guidebook on gaining the assent of children to participate in a trial. "While children may be legally incapable of giving informed consent, they nevertheless may possess the ability to assent to or dissent from participation. Out of respect for children as developing person, children should be asked whether or not they wish to participate in the research, particularly if the research: (1) does not involve interventions likely to be of benefit to the subjects; and (2) the children can comprehend and appreciate what it means to be a volunteer for the benefit of others. The [Ethics Committee] must determine for each protocol – depending on such factors as the nature of the research and the age, status and condition of the proposed subjects – whether all or some of the children are capable of assenting to participation. Where appropriate the [Ethics Committee] may choose to review on a case-by-case basis whether assent should be sought from given individual subjects. Assent should be sought when, in the judgement of the [Ethics Committee], the children are capable of providing their assent. [Ethics Committees] are to take into account the ages, maturity and psychological state of the children involved." (IRB, 1996:12)

[6] Clinical trials involving pregnant women or nursing mothers should ideally involve products where the toxicology in adults is established and is acceptable. In the case of pregnant women the potential risks associated with using a substance whose short term and long term effects on a foetus and developing infant are unknown, should be outweighed by the benefits. An example of a positive risk benefit ratio would be the use of anti-retrovirals in mother to child HIV transmission studies. For nursing mothers, the amount of drug passing into breast milk should be established and the potential impact on a breast fed infant anticipated, and the mother so advised.

[7] UNAIDS define vulnerable communities as having some or all of the following characteristics: Limited economic development; Inadequate protection of human rights and discrimination on the basis of the health status; Inadequate community/cultural experience with the understanding of scientific research; Limited availability of health care and treatment options; Limited ability of individuals in the community to provide informed consent.

3. Responsibility of the Principal Investigator & Participating Investigators - Contents

- 3.1 Competencies & Responsibilities of the Principal Investigator
- 3.2 Qualifications and Availability
- 3.3 Adequate Resources
- 3.4 Medical Care of Trial Participants
- 3.5 Informed Consent
- 3.6 Investigational Products
- 3.7 Compliance with Protocol
- 3.8 Monitoring and Auditing
- 3.9 Change of Principal Investigator
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- 3.14 Progress Reports
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3. RESPONSIBILITY OF THE PRINCIPAL INVESTIGATOR (PI) AND PARTICIPATING INVESTIGATORS

In most cases, clinical trials are conducted by a principal investigator (usually, but not limited to, a medical doctor with appropriate qualifications to undertake the study) who has entered an agreement with a sponsor to conduct a clinical trial. She/he is the person responsible for the conduct of the clinical trial at the trial site/s. Clinical trials, including multicentre studies, must be undertaken by local PI resident in South Africa.

A clinical trial can however be conducted with or without a sponsor. If a sponsor is involved in the clinical trial, the trial must be designed, conducted and reported in collaboration with both the sponsor and the principal investigator. If there is no sponsor, the principal investigator must clearly state in the protocol who takes on the role of the sponsor in the initiation, management and / or funding of the clinical trial.

The following section outlines the responsibilities of the principal investigator and other investigators designated by the principal investigator to undertake certain trial related activities in the conduct of clinical trials.

3.1 COMPETENCIES AND RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR

Prior to commencement of the trial, the PI must:

- be a South African based scientist;
- ensure that approval(s) from the relevant approved local ethics committee, and, if applicable, the MCC are obtained and that the trial is issued a study number by the National Health Research Ethics Council;
- have read and accepted the relevant information package developed by the sponsor for clinical studies;
- have good knowledge of the protocol, related documents and the regulatory requirements of the regulatory authority(ies) and other relevant legislation;
- have read, understood and agreed to work according to the protocol, the Declaration of Helsinki, ICH Guideline for Good Clinical Practice, these Guidelines and other relevant legislation;
- undertake to use the investigational and comparator product(s) only for the purposes of the study as described in the protocol;
- take responsibility for accountability of the investigational product(s);
- document clearly the sequence of events to be followed in the conduct of the clinical trial, including timeframes, roles and responsibilities;
- ensure the availability of all necessary facilities, equipment, and finance to conduct the trial;
- develop proper mechanisms to ethically obtain informed consent of participants;
- accept the involvement of monitors to review and verify the quality control procedures

- and conduct data verification;
- accept the possibility of audit and/or inspection by an independent auditor appointed by the sponsor, regulatory authority or ethics committee;
- obtain the right to publish; it is unethical for the sponsor to reserve to right to publish;
- generate the information package for the participant, and where applicable with the sponsor;
- ensure proper safety reporting procedures.

3.2 QUALIFICATIONS AND AVAILABILITY

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

The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure,⁸ in the product information and in other information sources provided by the sponsor.

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

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

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

3.3 ADEQUATE RESOURCES

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

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

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

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

3.4 MEDICAL CARE OF TRIAL PARTICIPANTS

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

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

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

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

respecting the subject's rights.

3.5 INFORMED CONSENT

The PI is responsible for ensuring that an adequate information package, in an acceptable format, is available for use in the process of seeking informed consent from participants to participate in the study. In all instances both written and verbal informed consent should be obtained. Verbal consent, where the participant is illiterate, should be obtained in the presence of and countersigned by a literate witness.

The PI, co-investigator, or designated person as defined in the protocol, should then seek the participant's informed consent to participate in the study in accordance with the principles outlined in the Declaration of Helsinki, and in these guidelines.

If the trial is a multi-site, and/or multi-country study, the site PI must ensure that informed consent procedures take cognisance of the characteristics of the site participants and tailor the informed consent content and procedures accordingly.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to participants should include explanations of the following:

- a. That the trial involves research.
- b. The purpose of the trial.
- c. The trial treatment(s) and the probability for random assignment to each treatment (where appropriate).
- d. The trial procedures to be followed, including all invasive procedures.
- e. The subject's responsibilities.
- f. The fact that participation in the trial is voluntary and refusal to participate or withdrawal from the trial will not prejudice the ongoing care of the person in any way.
- g. Those aspects of the trial that are experimental.
- h. The foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant. (Section 2.3.3 refers)
- i. The expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this. (e.g. Phase I Clinical Trial)
- j. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- k. The compensation and/or treatment available to the subject in the event of trial-related injury.
 - l. The anticipated prorata payment, if any, to the subject for participating in the trial.
- m. The anticipated expenses, if any, to the subject for participating in the trial.
- n. Allow access of sponsor or regulatory authority to patient records.
- o. Provide a contract name and number of the PI and directly responsible investigator.
- p. The identity of a sponsor and any potential conflict of interests.

Once consent to participate in the study has been obtained, a copy of the signed informed consent form and a source document identifying the study and recording the dates of participation should be placed in the participant's medical record. The original signed informed consent form should be kept with the trial records and a copy of signed informed consent form should be provided to the participant.

If the participant can identify a usual medical practitioner, the principal investigator, should seek consent from the participant to inform their usual medical practitioner of their entry into the study. The principal investigator should only inform the medical practitioner on approval from the participant.

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

3.6 INVESTIGATIONAL PRODUCT(S)

Responsibility for investigational product(s) accountability at the trial site(s) rests with the

investigator.

Investigational products which are unregistered medicines may only be brought into the country after the protocol has been approved by the regulatory authority. Samples of the investigational product imported before trial approval require a permit from the regulatory authority.

Where allowed/required, the investigator may/should assign some of the investigator's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

The investigator and/or a pharmacist or other appropriate individual, who is designated by the investigator, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s).⁹ These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial participants. Investigators should maintain records that document adequately that the participants were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

The investigational product(s) should be stored as specified by the sponsor, and in line with Good Pharmacy Practice (GPP) in South Africa, and the regulatory authority regulations and conditions.

Investigational products unused at the conclusion of a trial should be disposed of in line with the guidelines established by the regulatory authority.

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

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

3.7 COMPLIANCE WITH PROTOCOL

The investigator should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval by the ethics committee. The investigator and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

The investigator should not implement any changes to the protocol without agreement by the sponsor and prior review and documented approval from the ethics committee and the MCC of such amendment. An exception to this would be where it is necessary to eliminate an immediate hazard(s) to trial participants, or when the change(s) involve only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)). The regulatory authority and the ethics committee should be informed of any such changes in retrospect.

The investigator, or person designated by the investigator, should document and explain any changes to the approved protocol.

Where necessary, the investigator may implement a change to, the protocol to eliminate an immediate hazard(s) to trial participants without prior ethics committee/MCC approval. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be documented and submitted:

- a. to the ethics committee for review and approval,
- b. to the sponsor for agreement and,
- c. to the regulatory authority(ies).

For more detailed information on clinical trial protocol refer to Appendix B.

3.8 MONITORING AND AUDITING

The relationship between the principal investigator, the monitor and the sponsor must be clearly defined and stated in writing in the study protocol or related documents. These documents should also define a list of essential documents and detail how they are to be handled and stored. The investigator(s) should attend the initial briefing between the monitor and all staff involved in the study and be available for periodic visits by the monitor(s).

In addition, the investigator(s) should accept the possibility of audit and/or inspection by the sponsor, regulatory authority or ethics committee.

3.9 CHANGE OF PRINCIPAL INVESTIGATOR

If the principal investigator withdraws for any reason(s) before completion of the study, a suitably qualified successor should be appointed by the sponsor to take over responsibility for the conduct of the study.

Before the study continues, information about the new principal investigator (in similar form to that submitted for the original investigator) should be presented for approval to the relevant ethics committee. If practicable the change in principal investigator should also be notified to the participants in the study and the regulatory authority.

3.10 DATA MANAGEMENT

The principal investigator is responsible for the collection, quality, recording, maintenance and retrieval of source data arising from the clinical study. A fully comprehensive collection of information on the participant, the administration of the investigational product(s) and the outcome of the protocol procedures should be developed using Case Report Forms (CRF). The design of the CRF should facilitate observation of the participant and should be consistent with the protocol for the study. The protocol should specify which data will be entered directly into the CRF and will not be supported by other source data. The source document must be signed and dated by the clinician identified in the protocol, or designated person, on a visit by visit basis and then stored securely.

The principal investigator should make the data available to the sponsor/nominee to enable the conduct of data editing and audit according to the protocol/contract.

Corrections to CRFs can only be made by the principal investigator, co-investigator or designated person. Where existing data are incorrect, a single line should be drawn through the data in such a way that the original entry is not obscured, and the correct data inserted nearby. All corrections should be initialled and dated by the corrector.

Data collected by direct entry onto a computer should only be entered by the investigator and or a designated person. The computer system should be virus proofed, access restricted and should ideally record a data trail of all changes made to CRFs. The system should be designed in such a way that the data changes are documented and that there is no deletion of entered data in order to maintain, audit and edit data trail. Once a hard copy of the computer stored data has been made, procedures for editing are as for paper CRFs.

The sponsor may maintain a separate record of requests for clarification and correction (monitor's notes).

The investigator must be available for agreed visits by the monitor during the study and also co-operate in the data editing, quality control and audit.

3.11 SAFETY ISSUES

Decisions and actions relevant to the clinical management and safety of the participant in acute situations are the responsibility of the investigator. The investigator is responsible for ensuring that adequate provisions are made for dealing with any unexpected adverse events that may occur in the study participants. In some situations it may be appropriate for the sponsor to

develop standard operating procedures for the clinical management of some adverse events. These operating procedures should be included in the protocol and its related documents.

During the progress of the study the investigator is obliged to be acquainted with, and consider, new data on the investigational product, either supplied by the sponsor or published.

3.12 REPORTING OF SERIOUS ADVERSE EVENTS

The principal investigator must inform the sponsor, within the time specified in the protocol, of any serious or unexpected adverse events occurring during the study. A serious adverse event initial report form and any relevant follow-up information should be sent to the sponsor, who in turn should forward the relevant information to the appropriate ethics committee, and regulatory authority. A serious adverse event should be reported within 24 hour, whilst unexpected AEs must be reported without undue delay. (Section 4.19 refers)

3.13 PREMATURE TERMINATION - BREAKING THE TREATMENT CODE

The investigator should follow the trial's randomisation procedures, if any, and should ensure that the code is broken only in accordance with the protocol. In blinded studies the circumstances under which the code would be broken and the procedure for unmasking the identity of the treatment received by each participant should be stated in the protocol and known by the staff involved in the clinical management of the participants.

The principal investigator and/or a designated person should keep the treatment code list, code-break envelopes or code-break cards accessible 24 hours a day at the study site in the event of an emergency.

If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

Reporting of accidental unblinding or unblinding due to a serious adverse event should be reported to the regulatory authority by the principal investigator via the sponsor where there is a sponsor, in writing and within 24 hours of the incident.

3.14 PROGRESS REPORTS AND FINAL STUDY REPORTS

The investigator is obliged to submit progress reports as required by the sponsor, the regulatory authority and/or the relevant ethics committee(s). These reports should contain information on how the study is progressing, the number of participants included in relation to the number expected, the number of dropouts and withdrawals and if the planned time schedule is still appropriate. A final report on completion of the study should also be submitted. The format and frequency of reporting shall be as prescribed.

3.15 TRIAL OUTCOME

All trials should be analysed. The results of trials must be submitted to the Department of Health via National Health Research Ethics Council irrespective of the outcome of the trial. This is a condition of approval for any clinical trial being undertaken in South Africa.

Footnotes Chapter 3

[8] See ICH Guidelines:- Section 7: Investigator's Brochure for a more detailed discussion of the contents of the Investigator's Brochure.

[9] If it is a new investigational product, the MCC will specify the conditions under which the product is made available in South Africa.

4. Responsibilities of the Sponsor - Contents

- 4.1 Submission to MCC for Regulatory Authority Approval
 - 4.2 Confirmation of Review by Ethics Committees
 - 4.3 Registration with the Department of Health
 - 4.4 Quality Assurance and Quality Control
 - 4.5 Contract Research Organisation (CRO)
 - 4.6 Medical Expertise
 - 4.7 Trial Design
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 - 4.9 Investigator Selection
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 - 4.13 Financing
 - 4.14 Information on Investigational Products
 - 4.15 Manufacturing, Packaging, Labelling and Coding of Investigational Products
 - 4.16 Supplying & Handling of Investigational Products
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 - 4.19 Adverse Drug Reaction Reporting
 - 4.20 Premature Termination
 - 4.21 Reporting and Release of Trial Results
 - 4.22 Publication of Trial Results
 - 4.23 Non-compliance Procedures
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4. RESPONSIBILITIES OF THE SPONSOR¹⁰

A sponsor is the person or organisation responsible for the initiation, management or financing of a clinical trial (IRB:1993). A sponsor can be a pharmaceutical company, the principal investigator, a funding body or an individual or organisation designated by the funding body or principal investigator. It is important that sponsor's roles and responsibilities to be undertaken must be clearly articulated in the protocol and related documents.

To follow is a description of the roles and responsibilities of the sponsor in the conduct of clinical trials in South Africa. Some of these roles and responsibilities are repeated in the section on the responsibilities of the PI.

4.1 SUBMISSION TO THE MCC FOR REGULATORY AUTHORITY APPROVAL

Before initiating a clinical trial(s), the sponsor and the investigator, should submit the required MCC application(s) to the regulatory authority for review and permission to begin the trial(s). The protocol should be submitted in triplicate. It is the responsibility of both the sponsor and the PI to ensure that the protocol satisfies the requirements of the protocol checklist (Appendix D). Applicants should note that the MCC review process takes approximately 10 weeks.

In the event that regulatory authority approval is required for a drug trial in less than 10 weeks, fast track approval can be applied for, such approval may be sought when:

- The trial is for a new chemical entity or new indication which may be life saving or may represent a therapeutic breakthrough for a particular condition;
- For trials where the season is important and a delay would prevent the trial from progressing;
- Under exceptional circumstances for reasons of logistics.

4.2 CONFIRMATION OF REVIEW BY ETHICS COMMITTEE

The sponsor should obtain from the investigator the name and address of the investigator's relevant approved ethics committee and documented ethics committee approval.

If the ethics committee conditions its approval upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to participants, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval was given by the ethics committee.

The sponsor should obtain from the investigator documentation and dates of any ethics committee reapprovals/re-evaluations, and of any withdrawals or suspensions of approval.

4.3 REGISTRATION WITH NATIONAL HEALTH RESEARCH ETHICS COUNCIL

The sponsor must also obtain from the investigator a study number issued by the National Health Research Ethics Council. The study number is issued once the National Health Research Ethics Council has received a copy of approvals from an ethics committee, and if required, from the MCC.

4.4 QUALITY ASSURANCE AND QUALITY CONTROL

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs) to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the sponsor with the principal investigator and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

4.5 CONTRACT RESEARCH ORGANIZATION (CRO)

A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

The CRO, to which trial related duties have been delegated, must have the required skills, experience and competencies to conduct clinical trials.

Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

CROs must be regulated by MCC, registered with MCC, and pay a registration fee.

All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

4.6 MEDICAL EXPERTISE

The sponsor should designate appropriately qualified medical personnel who will be readily

available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose. (See section on PI responsibilities).

4.7 TRIAL DESIGN

The sponsor should utilise qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analysing and preparing interim and final clinical trial reports.

If the study is a multicentre and / or multi-country study, any differences in trial designs between the South African site and other sites, must be clearly documented and explained in the study protocol and related documents. (See section on PI responsibilities)

4.8 TRIAL MANAGEMENT, DATA HANDLING, AND RECORD KEEPING

The sponsor should utilise appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

- a. Ensure and document that the electronic data processing system(s) conform(s) to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).
- b. Maintains SOPs for using these systems.
- c. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).
- d. Maintain a security system that prevents unauthorized access to the data.
- e. Maintain a list of the individuals who are authorized to make data changes.
- f. Maintain adequate backup of the data.
- g. Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

The sponsor should use an unambiguous subject identification code that allows identification of all the data reported for each subject.

The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial.

The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of South Africa.

If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 5 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

The sponsor specific essential documents should be retained for not less than 5 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

4.9 INVESTIGATOR SELECTION

The sponsor is responsible for selecting the investigator(s). Each investigator should be qualified by training and experience and should have adequate resources to properly conduct the trial for which the investigator is selected. If the organisation of a coordinating committee and/or selection of coordinating investigator(s) are to be utilised in multicentre trials, their organisation and/or selection are the sponsor's responsibility.

Before entering an agreement with an investigator to conduct a trial, the sponsor should provide the investigator(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator to review the protocol and the information provided.

The sponsor should obtain the investigator's agreement:

- a. to conduct the trial in compliance with GCP, these guidelines, the requirements of the regulatory authority and with the protocol agreed to by the sponsor and given approval by the relevant ethics committee;
- b. to comply with procedures for data recording/reporting;
- c. to permit monitoring, auditing and inspection; and
- d. to retain the trial related essential documents until the sponsor informs the investigator/institution that these documents are no longer needed.

The sponsor and the investigator should sign the protocol, or an alternative document, to confirm this agreement.

4.10 ALLOCATION OF RESPONSIBILITIES

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions. These must be clearly documented in the protocol related documents.

4.11 COMPENSATION TO PARTICIPANTS AND INVESTIGATORS¹¹

The MCC requires that all participants in clinical trials are covered by comprehensive insurance for injury and damage.

Notwithstanding the absence of legal commitment, the sponsor should pay compensation to patient-volunteers suffering bodily injury, including death, in accordance with these guidelines.

Compensation should be paid when, on the balance of probabilities, the injury was attributable to the administration of a medicinal product under a trial or any clinical intervention or procedure provided for by the protocol that would not have occurred but for the inclusion of the patient in the trial.

Compensation should be paid to a child injured in utero through the participation of the subject's mother in a clinical trial as if the child were a patient-volunteer with the full benefit of these guidelines.

Compensation should only be paid for the more serious injury of an enduring and disabling character (including exacerbation of an existing condition) and not for temporary pain or discomfort or less serious or curable complaints.

Where there is an adverse reaction to a medicinal product under trial and injury is caused by a procedure adopted to deal with that adverse reaction, compensation should be paid for such injury as if it were caused directly the medicinal product under trial.

Neither the fact that the adverse reaction causing the injury was foreseeable or predictable, nor the fact that the patient has freely consented (whether in writing or otherwise) to participate in the trial should exclude a patient from consideration for compensation under these guidelines.

For the avoidance of doubt, compensation should be paid regardless of whether the patient is able to prove that the sponsor has been negligent in relation to research or development of the medicinal product under trial or that the product is defective and therefore, the sponsor is under strict liability in respect of injuries caused by it.

No compensation should be paid:

- For the failure of a medicinal product to have its intended effect or to provide any other benefit to the subject.
- For injury caused by other licensed medicinal products administered to the patient of the purpose of comparisons with the product under trial.
- To patients receiving placebo in consideration of its failure to provide a therapeutic benefit.
- (or it should be abated as the case may be) to the extent that the injury has arisen through:
 - a significant departure from the agreed protocol
 - the wrongful act or default of a third party, including a doctor's failure to deal adequately with an adverse event
 - through contributory negligence by the patient.

The amount of compensation should be paid appropriate to the nature, severity and persistence of the injury and should in general terms be consistent with the quantum of damages commonly awarded for similar injuries by a South African Court in cases where legal liability is admitted.

Compensation should be abated, or in certain circumstances excluded, in the light of the following factors (on which will depend the level of risk the patient can reasonably be expected to accept):

- the seriousness of the disease being treated, the degree of probability that adverse reactions will occur and any warning given
- the risks and benefits of the established treatments relative to those known or suspected of the trial medicines.

This reflects the fact that flexibility is required given the particular patient's circumstances. As an extreme example there may be patient suffering from a serious or life-threatening disease who is warned of certain defined risk of adverse reaction. Participation in the trial is then based on an expectation that the benefit/risk ratio associated with participation may be better than that associated with alternative treatment. It is, therefore, reasonable that the patient accepts the high risk and should not expect compensation for the occurrence of the adverse drug reaction of which he or she was told.

In any case where the sponsor concedes that payment should be made to a patient but there exists a difference of opinion between sponsor and patient as to the appropriate level of compensation, it is recommended that the sponsor agrees to seek at its own cost (and make available to the patients) the opinion of a mutually acceptable independent expert, and that his/her opinion should be given substantial weight by the sponsor in reaching its decision on the appropriate payment to be made.

Claims in pursuant to the guidelines should be made by the patient to the sponsor, preferably via the investigator, setting out details of the nature and background of the claim and, subject to the patient providing on request an authority for the sponsor to review any medical records relevant to the claim, the sponsor should consider the claim expeditiously.

The undertaking given by a sponsor extends to injury arising (at whatever time) from all administrations, clinical interventions or procedures occurring during the course of the trial but not to treatment extended beyond the end of the trial at the instigation of the sponsor. The use of unlicensed products beyond the trial is wholly the responsibility of the treating doctor. The MCC must be informed in writing of any such activities.

The fact that a sponsor has agreed to abide by these guidelines in respect of a trial does not affect the right of a patient to pursue a legal remedy in respect of injury alleged to have been suffered as a result of participation. Nevertheless, patients will normally be asked to accept that any payment made under the guidelines will be in full settlement of their claims. Clinical trials insurance in no way replaces a clinician's malpractice insurance.

4.12 TRIAL INCENTIVES

The sponsor must ensure that information on incentives offered to participants involved in the trial is included in the protocol. If the study is multi-centered, information on the incentives given to participants at all the different trial sites, irrespective if these are multinational, must also be provided. Differences in the incentives across sites must be explained.

The sponsor must also ensure that participants are reimbursed for all reasonable costs incurred by their participation in the trial.

4.13 FINANCING

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

A declaration must be signed by both the sponsor and the principal investigator which states that there are sufficient funds available to complete the study.

4.14 INFORMATION ON INVESTIGATIONAL PRODUCT(S)

When planning trials, the sponsor should ensure that sufficient safety and efficacy data from pre-clinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

The sponsor should update the Investigator's Brochure as significant new information becomes available.

4.15 MANUFACTURING, PACKAGING, LABELLING, AND CODING INVESTIGATIONAL PRODUCT(S)

The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterised as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. The labelling should comply with MCC requirement(s). (e.g. Labels of materials used in clinical trials should clearly state that it is clinical trial material, provide information on the manufacture and expiry date and give sponsor contact details).

The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. Compliance with the GPP, where applicable, will be required. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

4.16 SUPPLYING AND HANDLING INVESTIGATIONAL PRODUCT(S)

The sponsor is responsible for supplying the investigator with the investigational product(s).

The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval from the appropriate ethics committee and regulatory authority(ies)).

The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from participants, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorised by the sponsor and in compliance with the applicable regulatory requirement(s)).

The sponsor should:

- a. Ensure timely delivery of investigational product(s) to the investigator(s).
- b. Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s).
- c. Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).
- d. Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition. Disposal must be done according to the regulation of the regulatory authority.

The sponsor should:

- a. Take steps to ensure that the investigational product(s) are stable over the period of use.
- b. Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

4.17 RECORD ACCESS

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review, and regulatory inspection.

The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, ethics committee review, and regulatory inspection.

4.18 SAFETY INFORMATION

The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

The sponsor should promptly notify, in writing all concerned investigator(s) and the regulatory authority and ethics committee of findings that could affect adversely the safety of participants, impact the conduct of the trial, or alter the ethics committee's approval/favourable opinion to continue the trial.

4.19 ADVERSE DRUG REACTION REPORTING

The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the ethics committee(s), and to the regulatory authority of all adverse drug reactions (ADRs) that are both serious and unexpected.

A serious adverse drug reaction should be reported within 24 hour, whilst unexpected ADRs must be reported without undue delay.

If the study is multi-centred, the sponsor should ensure that all serious and unexpected adverse drug events that occur in other study sites are also reported without delay on six monthly basis to all appropriate parties including, investigator(s), ethics committee(s), and to the regulatory authority.

The sponsor should submit to the regulatory authority and ethics committees all safety updates and periodic reports, as required by applicable regulatory requirement(s). Review of reported serious and unexpected adverse drugs events need to include analysis, evaluation and complete account of the entire body of safety information of the drug, as such data may have emerged during the course of clinical trials by the PI and in the international data set.

4.20 PREMATURE TERMINATION

The sponsor must ensure that the procedures for unblinding on the account of adverse events or by accident, and the premature termination of a trial is clearly documented within the study protocol. Such events must be reported to all concerned investigator(s)/institutions(s), to the ethics committee(s), and to the regulatory authority.

4.21 REPORTING AND RELEASE OF TRIAL RESULTS

The sponsor is responsible for ensuring that trial activities and outcomes are routinely reported to the appropriate ethics committee and the regulatory authority.

The results of all trials must be communicated to the appropriate ethics committee, the regulatory authority and the Director General of Health. The sponsor and the principal investigator are responsible for the appropriate dissemination of the trial findings.

The sponsor must notify the regulatory authority of all Phase IV trials.

4.22 PUBLICATION OF TRIAL RESULTS

The principal investigator has a duty and right to publish trial results, irrespective of the sponsor's consent. Trial results should always be reported to the appropriate ethics committee, the regulatory authority and the National Health Research Ethics Council.

4.23 NON-COMPLIANCE PROCEDURES

The sponsor has an ethical duty to inform the appropriate ethics committee and regulatory authority of possible instances of serious contravention of GCP during the course of a clinical trial that affect participant's safety, the credibility of data and/or the ethics of the trial.

Footnotes Chapter 4

[10] Unless otherwise specified by way of *italics*, the bulk of this section has been taken directly from the ICH

Harmonised Guideline. Guideline for Good Clinical Practice, May 1996.

[11] Association of the British Pharmaceutical Industry Compensation Guidelines

5. Quality Assurance - Contents

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5. QUALITY ASSURANCE

Quality assurance has been defined as, "All those actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with these guidelines ... and the applicable regulatory requirements."¹² Quality assurance of clinical trials in South Africa is achieved at a number of levels, through monitoring, audits and inspections.

5.1 THE MONITOR

The monitor is appointed by the sponsor and is an important communication link between the sponsor and the investigator(s).

5.1.1 Responsibilities of the Monitor

The main responsibility of the monitor is to oversee and report on the progress of a study. The monitor should follow standard operating procedures (SOPs) to ensure that a study is conducted and reported in accordance with the protocol, SOPs, and appropriate legislation.

The monitor should ideally have adequate medical, pharmaceutical and/or scientific qualifications. Acceptable qualifications for a monitor depend upon the type of study and the investigational product. The monitor should be fully cognisant of the product under investigation, clinical research procedures and the requirements of the protocol and related documents.

A written record should be kept of the monitor's visits, telephone calls and letters to the investigator.

The monitor or other contact person, appointed by the sponsor and known to the

investigator and co-investigator, should be available at any time for consultation or reporting of serious adverse events.

5.1.2 Prior to Commencing the Study

Prior to the start of the study the monitor should visit the principal investigator to verify that the site, staff and facilities for the study comply with the requirements of the protocol and sponsor SOPs. The monitor may be accompanied by the sponsor's staff during this visit.

Laboratories participating in the study should be checked by the monitor to ensure that they are accredited by an appropriate accreditation organisation and that they have adequate quality assurance.

5.1.3 Contacts with the principal investigator and co-investigator(s)

The monitor should ascertain:

- the qualifications of the principal and co-investigator(s), i.e. written curriculum vitae;
- the principal and co-investigator's understanding of the data on the investigational product, including pharmaceutical, pre-clinical and if appropriate, clinical data (investigator's brochure);
- the investigator(s) awareness of their obligations in undertaking the study;
- that the investigator(s) agree to conduct the clinical study in accordance with the protocol, Declaration of Helsinki, SOPs, relevant legislation and good clinical research practice;
- that the investigator(s) will accept the relevant controls, including data verification procedures, audit and/or inspection;
- that each investigator has the means necessary to carry out the study safely with regard to factors such as availability of participants for recruitment, facilities, medical, paramedical staff and clerical support; and
- the compatibility of the proposed study with the principal and co-investigator's research and other commitments.

The monitor should also:

- inform each principal investigator of the names of the other principal investigators working on the same protocol in South Africa and other principal investigator(s) overseas;
- check that storage, dispensing and documentation of the supply of investigational product(s) is safe and appropriate and in accordance with local regulations and SOPs;
- explain the treatment code and the procedures for breaking of the code, under conditions described in the protocol and how to reach the appropriate person(s) in an emergency;
- ascertain the membership of the ethics committee and check that it is approved by the National Health Research Ethics Council;
- confirm that the regulatory requirements, ethics committee review procedures and informed consent procedures are followed and recorded;
- inform the investigator(s) of the established requirements concerning the retention of records and retrieval of data (see also section 9);
- discuss in detail the protocol and protocol related documents prior to obtaining the principal investigator's signed approval;
- check the descriptions of the methods, normal and reference values for the tests to be performed during the study;
- provide the principal investigator with written information suitable for developing the patient information package;
- obtain a copy of the relevant approval(s) from the local ethics committee and, where applicable, clinical institution prior to study commencement;

- obtain a copy of relevant approval from the regulatory authority; and
- obtain a copy of the study number issued by the National Department of Health.

5.1.4 Contacts with staff

The monitor should check that all staff involved in the study are informed about its scope and procedures by:

- obtaining a signed and dated list of names of the staff directly involved in the study and a description of the functions of each person in the study;
- making contact with the senior doctor or head of department/centre who is responsible for research and receive assurance that the study is compatible with the work at the study site from both medical and administrative points of view; and
- discussing, preferably at a single meeting, the study protocol and the conduct of the study with the staff involved and their superiors e.g. medically responsible senior doctor or head of department/centre.

Immediately prior to the proposed starting date it is advisable for the monitor to visit the study site to ensure the investigator has all the required materials, e.g. CRFs, investigational product supplies, consent forms and information leaflets.

5.1.5 During the Course of the Study

The monitor should maintain personal contact with the principal investigator by visiting the study site regularly and, if necessary, assemble and meet with the participating staff. The frequency of these visits will depend on the SOPs, the number of participants involved and the nature of the study.

The monitor should ensure:

- that each investigator has access to a mechanism to identify the treatment of a particular participant;
- that informed consent for each participant has been obtained prior to commencement of any protocol required activity for that participant;
- that all investigational products are used according to the conditions in the protocol;
- that participant compliance is properly documented;
- that the investigator retains all necessary study documentation;
- that source data are available, to ascertain the existence of the participant and enable information recorded in the CRFs, e.g. biological results, radiographs, to be verified where possible. The source data should also be checked for correct labelling, dating, signatures, etc. (Source data may be the original or a signed and verified copy, as agreed with the sponsor). Access to source data must take place within the requirements of the privacy legislation and is dependant on the express informed consent of the participant which may be collected at the time of original enrolment into the study ;
- that any changes to the CRFs are properly documented, signed and dated;
- that any problems which arise in the course of the study, or may be foreseen, are discussed; and
- that the investigational product(s) are managed in accordance with Section 4 and that full dispensing or distribution records of the investigational product(s) are maintained.

The monitor must make every effort to maintain confidentiality of information about the participant, including the participant's identity when checking documentation. The monitor should ensure that all information relating to an individual participant is collected and stored by the investigator in compliance with the privacy

legislation.

Completed and signed CRFs should be collected during the course of the study or immediately upon their completion or in the event of premature termination of a study.

The monitoring visit should normally include an evaluation of:

- the progress of the study, determination of recruitment status, number of withdrawals and adverse events;
- the activities of the principal investigator and his or her staff and the continuing ability of the centre to participate in the study;
- adherence to the protocol and related documents. In particular the monitor should make an effort to obtain maximum information on any missing or unclear data;
- the conformity of the data presented in the CRFs with source data;
- the essential documents to ensure that they are being correctly filled in and stored in compliance with the protocol;
- monitoring (including observation where appropriate) of the informed consent procedure.

The monitor should check that a report is prepared regularly to fulfil the reporting requirements of the sponsor, ethics committees and regulatory authority.

The monitor should inform and discuss with the principal investigator and co-investigators the possible effects on the safety or ethics of the study of any new data relating to the investigational product(s). All proposed protocol amendments must have the agreement of both the principal investigator and sponsor, and any information which is felt to have a significant effect on the safety or the ethics relating to the study should be presented to the relevant accredited ethics committee by the investigator.

A separate report for the sponsor, the ethics committee and the regulatory authority should be written by the monitor after completion of each visit for each study and each site. This report should be written in accordance with a standard operating procedure and should accurately reflect the discussions with the relevant investigator/personnel stating the findings, conclusions/corrections and actions taken.

5.1.6 After Completion of the Study

When a study is completed the monitor should ensure:

- that complete documentation of all clinical and laboratory investigations is available in the CRFs;
- that all CRFs are collected and placed for safe keeping in accordance with regulatory requirements, privacy legislation and the sponsor's operating procedures;
- that the principal investigator has notified the study participants, ethics committees and, if required, regulatory authorities that the study has been completed;
- that treatment codes are collected, recording all cases where the treatment code has been broken and the reasons for doing so;
- that the principal investigator is aware of the archiving requirements for source data and primary records;
- that the standard operating procedure for unused supplies of the investigational product(s) is followed, i.e. unused supplies are collected or destroyed; that an appropriate record is kept in collaboration with the pharmacist or person designated as responsible for handling the investigational product(s); and

- that the study information is collated and sent to the reporting centre for multi-national studies.

5.2. AUDIT

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.2.1 Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, GPP, Good Laboratory Practices (GLP - where appropriate) and the applicable regulatory requirements.

5.2.2 Selection and Qualifications

The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.2.3 Auditing Procedures

The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of participants in the trial, the type and complexity of the trial, the level of risks to the trial participants, and any identified problem(s).

The observations and findings of the auditor(s) should be documented and accessible to the ethics committee and / or the regulatory authority.

The person responsible for auditing must submit a report to the regulatory authority(ies) when evidence of GCP non-compliance exists, or in the course of legal proceedings.

When required by applicable law or regulation, the sponsor should provide an audit certificate.

5.2.4 Non-compliance

Noncompliance with the protocol, SOPs, GCP, GLP, GPP and/or applicable regulatory requirement(s) by an investigator, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator, the sponsor should terminate the investigator's participation in the trial. When an investigator's participation is terminated because of noncompliance, the sponsor should promptly notify the regulatory authority(ies).

5.2.5 Premature Termination or Suspension of a Trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators, and the regulatory authority(ies) of the termination or

suspension and the reason(s) for the termination or suspension. The ethics committee should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator, as specified by the applicable regulatory requirement(s).

5.2.6 Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s).

5.3. INSPECTIONS (Appendix C)

As prescribed by regulations of the MCC (Medicines and Related Substances Act, 1965), the regulatory authority may inspect the conduct of a clinical trial by on-site visits. Inspections are reserved to situations where there is a reason to believe the competency of the clinical trial site needs review, or there is some evidence of GCP non-compliance. Inspectors have the power to conduct both announced and unannounced inspections.

Such an inspection should consist of a comparison of the procedures and practices of the clinical investigator with the commitments set out in the protocol and reports submitted to the regulatory authority by the investigator or the sponsor.

Inspections may be carried out randomly, and /or for specific reasons. MCC inspectors should be given easy access to the trial sites and laboratories at all times, announced or unannounced.

The inspection should determine whether the investigator has custody of the required records or, if not, who has assumed this responsibility. The archives should be tested for retrieval.

Inspections may include a data audit. The regulatory authority should have easy access to all patient files and raw data utilised for and generated during the trial.

All site data and documents must be available for verification. All observations and findings should be verifiable in order to ensure the credibility of data and to assure that the conclusions presented are derived correctly from the raw data. Verification processes must, therefore, be specified and justified.

Sponsor and investigational sites, facilities and laboratories, and all data (including source data) and documentation and reports concerning the data including subject files must be available for inspection by the regulatory authority.

Footnotes Chapter 5

[12] MRC Guidelines for Good Clinical Practice in Clinical Trials, 1998, 20 Park Crescent, London, W1N 4AL, United Kingdom

6. Data Management and Statistics - Contents

- 6.1 Protocol
- 6.2 Randomisation
- 6.3 Data Management
 - 6.3.1 Data Integrity and Transfer
 - 6.3.2 Case Report Form
 - 6.3.3 Data Quality Control
 - 6.3.4 Code Breaking for Data Analysis

- 6.4 The Final Study Report
- 6.5 Preservation of Records
- 6.6 Archiving by the Principal Investigator
- 6.7 Archiving by the Sponsor

6. DATA MANAGEMENT AND STATISTICS

Statistical considerations must be an integral part of study design and the description and analysis of the final results. The aim should be to integrate the clinical and statistical aspects as fully as possible through all phases of a clinical study.

Statisticians and data managers should have advisory and operative functions in the design of clinical studies, in reviewing study protocols, CRFs and manuscripts, and in the design of computer systems for data processing. The operative functions consist of writing or advising on statistical sections in protocols and reports, adapting or developing appropriate methods for the statistical analysis, performing the analysis and making the statistical interpretation of the results.

The protocol and the final study report should be reviewed and commented upon by a statistician.

6.1 PROTOCOL

Statistical considerations in a study protocol should be an integral part of the document and special attention should be paid to the following aspects:

- that the experimental design of the study is appropriate to the purpose of the study and the nature of the study condition;
- that the sample size is large enough to allow detection of clinically meaningful differences or to document clinical equivalence as appropriate, in variables specifically related to the hypotheses stated in the protocol;
- that the calculation of the sample size is based on sufficient statistical power and adequate levels of significance specified before commencement of the study;
- that the calculation of sample size takes into account any planned interim or sub-group analyses;
- that the randomisation procedures must be scientifically justified in the protocol;
- that for comparative, open-label studies measures taken to avoid bias are specified (preferably assigned by central randomisation);
- that the reasons and procedures for any planned interim analyses, whether used in sequential design for possible early termination or for any other purpose, are clearly specified in writing. It is advisable to have an independent supervisory committee to perform interim analyses to maintain study blindness among investigators and others involved;
- that the general approach to the statistical analysis is described, including methods of adjusting for possible imbalance in prognostic factors at baseline;
- that criteria which can be foreseen for including and/or removing participants from certain analyses are defined;
- that the use of intention-to-treat analysis and/or per protocol analysis is specified. (This will usually only apply to analyses of efficacy variables.);
- that methods for dealing with/analysing incomplete data (missing observations, premature withdrawals, etc.) are specified; and
- that specific statistical models and methods which can be foreseen are used even if some flexibility must be allowed at the time of analysis.

6.2 RANDOMISATION

In the case of randomisation of participants, the procedure must be documented. In a blinded, randomised study it is usually necessary to supply and keep the treatment code for each

individual participant at both the study site and with the sponsor.

The protocol must state when the treatment code for an individual participant may or may not be broken. Breaking the treatment code must be possible 24 hours a day in case of an emergency and the procedures and persons involved clearly designated in the protocol and related documents. The date, reasons for, and name of the individual breaking the study code must be documented.

Before the treatment code is broken for statistical analysis, the code for each participant must be returned to the sponsor with a documented explanation for each episode where the code was broken. Any master code supplied (e.g. to the pharmacy) must be returned to the sponsor. No copies of the code should be taken by any person involved in the study. Copies of the treatment code will be available to the investigator at the end of the study after the database is 'locked'.

6.3 DATA MANAGEMENT

The aim of data management is to turn the information from the participant, efficiently and without errors, into data in the statistical database.

All steps involved in data management should be part of a standard operating procedure and should be documented to allow for a step-by-step retrospective assessment of data quality and study performance; i.e. an audit trail. Documentation is facilitated by the use of such means as checklists and forms giving details of action taken, dates and the individuals responsible.

6.3.1 Data integrity and transfer

A basic aspect of the integrity of data is the safeguarding of "blindness" with regard to treatment assignment. It starts with the randomisation of participants into treatment groups and it is maintained through all steps of data processing up until the decision to break the code is formally taken.

The confidentiality of the database must be secured by appropriate standard operating procedures including passwords for all staff involved in the case of a computer database. The use of a computer system which logs who has had access to the information, and logs and dates all changes to the information is recommended. Satisfactory maintenance and back-up procedures for computer databases must be provided.

6.3.2 Case Report Form (CRF)

The design of the case report form should meet the specific data requirements set out in the study protocol. In addition, basic form design concepts should be adopted where feasible. Such concepts relate to consistency in the use of reference codes, terminology and format. Standardisation in the design of forms and computer programmes used in the data processing and statistical analysis will save time and prevent errors.

6.3.3 Data quality control

The aim of quality control procedures is to minimise the effects of missing and inaccurate data. The data editing process should be part of the standard operating procedures documentation which describe the process for confirmation and correction of data. The standard operating procedure for data editing should guarantee that any queries about data validation are brought rapidly to the attention of the investigators.

An audit trail should be available to trace the nature of any changes to data, the dates of changes and the person responsible for the changes.

Data collection and entry should be performed continuously during the course of the study. It should be checked either by double-entry (preferable) or by proof-

reading for the primary variables and on a random basis for other parameters.

Checks for validity and consistency of the database should be on separate items as well as on predetermined combinations of items in the CRFs.

Checks should be manual as well as computerised. In the latter case it should be combined with data entry (e.g. immediate automatic checks or batch checking) in order to speed up feed-back on data requiring clarification.

To supplement the continuous checking of each individual's data during the study, descriptive statistics on each important variable in the database (performed without breaking the code) are useful in the detection of doubtful and/or unusual data.

6.3.4 Code breaking for data analysis

When the validation and editing process is concluded the formal 'locking' of the database should be documented.

Data for each individual participant should be classified and coded with respect to its inclusion in the various statistical analyses planned in the study and the code entered into the data base.

After the above actions have been documented the treatment code can be broken and included in the data base for each individual participant.

6.4 THE FINAL STUDY REPORT

The protocol, statistical and clinical aspects should be integrated in order to obtain a final study report that is entirely consistent with the study data generated. Essential elements in the presentation of the results of a study of an investigational product are:

- baseline comparisons between the treatment groups;
- the number of participants actually randomised into the study by treatment group and the number of participants excluded from any of the analyses, by reason and by treatment group;
- major efficacy and safety results by treatment group in the form of tables, graphs, test variables and statistical parameters (e.g. p-values) as appropriate;
- an assessment of between-group differences with confidence intervals; and
- in multicentre studies, an evaluation of centre effect may be a valuable addition and should always be conducted where significant inter-centre variation is suspected.

An account must be made of missing, unused or spurious data during statistical analyses. All omissions of this type must be documented to enable review to be performed.

The final study report must be recorded in the database of the Director General of Health.

6.5 PRESERVATION OF RECORDS

Both the principal investigator and the sponsor are obliged to retain records and data from the study for safety reasons and for audit and inspection subsequent to study completion. The time frames depend on the nature and duration of the study and must conform to the requirements of the relevant privacy legislation and the South African Constitution. Acceptable archiving practices are 5 years for biological samples and 10 years for written materials. Samples, documents and any computer records should be retained in a secure place to prevent undue access, loss or tampering.

6.6 ARCHIVING BY THE PRINCIPAL INVESTIGATOR

The principal investigator is responsible for maintaining copies of all documentation which

contains identifying source data and other essential documentation including, the study protocol and amendments, applications to the ethics committee, serious adverse event reports and all other correspondence relating to the study.

All correspondence between the principal investigator and the sponsor must be preserved and be available on the request of the study sponsor, the regulatory authority, independent auditors or ethics committee. Investigational product accountability records detailing the storage and use of the product should also be retained.

Adequate steps must be taken to ensure that the hospital case records of all participants in clinical research are retained for this period, which is longer than the time to destruction interval in some hospitals and institutions.

If the principal investigator is unable to maintain custody of the study documents and samples, the sponsor should be informed in writing about the location of the records and the name of the person responsible for their retention. If necessary the sponsor may inventory and retain, in a sealed container, the investigator's documents. The means by which prompt access can be assured should also be stated.

6.7 ARCHIVING BY THE SPONSOR

The sponsor should retain copies of all essential documentation relating to the study which do not contain participant identifying information. These include reports to the regulatory authority, records of monitor-investigator contacts and investigational product supplies.

The files should also include information on the person(s) at the study site maintaining custody of the participant lists and responsibility for the archiving of the investigator's documents.

The period and conditions under which the documents should be saved is no different than those imposed on the investigator; i.e. at least 10 years after termination of the study and preferably for the commercial lifetime of the product.

Computer records must be reproduced in hard copy, which are to be signed and dated as a verified accurate copy of the original data. The verified hard copy should then be stored with other paper-based records, to overcome the possibility of loss or inability to read the information due to technological redundancy.

7. MULTI-CENTRED STUDIES

A multi-centred study is a study conducted simultaneously by several investigators at different centres, with standardised methods and protocol.

In South Africa, multi-centred trials must adhere to all national regulatory requirements.

Moreover, the design of the multi-centre trial must ensure that local realities are considered and well integrated into the design of the study. In particular the following must be addressed within the protocol:

- Inclusion and exclusion criteria must be appropriate for local realities
- Informed consent procedure must be tailored to local conditions
- Study design differences between South Africa site/s and other sites must be fully explained
- Awareness of the need to ensure that study extrapolations and conclusions are relevant to the South African context

To ensure these aspects and others are addressed within the protocol and that the proposed research is ethical, local investigators must always critically evaluate the protocol before submission to the regulatory authority.

The person responsible for the overall clinical care of the patient should be closely concerned with or informed of the running of the research project. This is to avoid any uncertainty on the part of others in the clinical team, if there should seem to be conflict between the apparent demands of the research protocol on the one hand and the interests of the individual patients on the other. At all times the patient's interests take precedence.

Except for in exceptional circumstances (with the permission of the Department of Health, DOH) the DOH would like to strengthen national institutions in conducting clinical trial research. Within this understanding, the principal investigator or overall project manager should be a South African based scientist. This condition also applies to collaborating projects with international research groups and multi-country studies. In the case of international (multi-centre) trials, there will be a requirement that a reasonable proportion of significant project team members (managers and technical experts) be South African based scientists.

Given these complexities, an independent steering committee should be established within country to ensure that the study is planned according to acceptable scientific and ethical standards. This committee must have access to study finding(s) and any adverse events. The roles and responsibilities of this steering committee should be clearly stated within the study protocol.

The steering committee and the sponsor should ensure that:¹³

- All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favourable opinion by the ethics committee.
- The CRFs are designed to capture the required data at all multi-centre trial sites.
- The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.
- All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.
- Communication between investigators is facilitated.

Footnotes Chapter 7

[13] ICH Harmonised Tripartite Guideline. Guidelines for Good Clinical Practice. Recommended for Adoption at Step 4 of the ICH Process on 1 May 1996 by the ICH Steering Committee

8. Ethics Committees - Contents

- 8.1 Responsibilities
 - 8.2 Composition, Functions and Operations
 - 8.3 Procedures
 - 8.4 Records
 - 8.5 Disclosure of Potential Conflict of Interest
-

8. ETHICS COMMITTEES

8.1 RESPONSIBILITIES

An ethics committee should safeguard the dignity, rights, safety, and well-being of all trial participants. Special attention should be paid to trials that may include vulnerable participants.

The ethics committee should obtain the following documents: trial protocol(s)/amendment(s),

written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to participants, Investigator's Brochure (IB), available safety information, information about payments and compensation available to participants, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the ethics committee may need to fulfil its responsibilities.

The ethics committee should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

- approval;
- modifications required prior to its approval;
- disapproval; and
- termination/suspension of any prior approval.

The ethics committee should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the ethics committee requests.

The ethics committee should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human participants, but at least once per year.

When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative the ethics committee should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible, the ethics committee should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e. in emergency situations).

The ethics committee should review both the amount and method of payment to participants to assure that both neither present problems of coercion or undue influence on the trial participants. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

The ethics committee should ensure that information regarding payment to participants, including the methods, amounts, and schedule of payment to trial participants, is set forth in the written informed consent form and any other written information to be provided to participants. The way payment will be prorated should be specified.

8.2 COMPOSITION, FUNCTIONS AND OPERATIONS

The ethics committee should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the ethics committee must be:

- Be representative of the communities they serve and reflect the demographic profile of the population of South Africa;
- have a minimum membership of at least seven members;
- have a chairperson;
- include members of both gender and not more than 70% of its members must be men or women;
- at least one lay person with no affiliations with the institution, not currently involved in medical, scientific or legal work and who are preferably from the community;
- at least one member with knowledge of, and current experience in areas of research that are regularly considered by the ethics committee;
- at least one member with knowledge of and current experience in the professional care,

counselling or treatment of people (e.g. medical practitioner, psychologist, social worker, nurse); and

- at least one member who is legally trained.

The ethics committee should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

Ethical review should be done in compliance with the Regulatory Authority checklist as outlined in Appendix B.

An ethics committee should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

Only members who participate in the ethics committee review and discussion should vote/provide their opinion and/or advise.

The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the ethics committee or in the vote/opinion of the ethics committee.

An ethics committee may invite nonmembers with expertise in special areas for assistance.

8.3 PROCEDURES

The ethics committee should establish, document in writing, and follow its procedures, which should include:

- Determining its composition (names and qualifications of the members) and the authority under which it is established.
- Scheduling, notifying its members of, and conducting its meetings.
- Conducting initial and continuing review of trials.
- Determining the frequency of continuing review, as appropriate.
- Providing, according to the applicable regulatory requirements, expedited review and approval of minor change(s) in ongoing trials that have the approval of the ethics committee.
- Specifying that no subject should be admitted to a trial before the ethics committee issues its written approval of the trial.
- Information to be provided to participants.
- The way payment will be prorated should be specified.
- Specifying that no deviations from, or changes of, the protocol should be initiated without prior written ethics committee approval of an appropriate amendment, except when necessary to eliminate immediate hazards to the participants or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)).
- Specifying that the investigator should promptly report to the ethics committee:
 - a. Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial participants
 - b. Changes increasing the risk to participants and/or affecting significantly the conduct of the trial
 - c. All adverse drug reactions (ADRs) that are both serious and unexpected. These should also be reported to the regulatory authority.
 - d. New information that may affect adversely the safety of the participants or the conduct of the trial.
- Ensuring that the ethics committee promptly notify in writing the investigator/institution concerning:
 - a. Its trial-related decisions.

- b. The reasons for its decisions.
- c. Procedures for appeal of its decisions.

8.4 RECORDS

The ethics committee should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 5 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The ethics committee may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

8.5 DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST¹⁴

Institutions including organisations sponsored to conduct clinical trials and Ethics Committees must have clearly formulated policies regarding conflicts of interest.

These institutions or organisations must formulate and advertise to their staff all policies and procedures regarding appropriate disclosure of affiliation with, or financial involvement in, any organisation or entity with a direct interest in the subject matter or materials of researchers. These procedures must cover the full range of potential interest, including the direct benefits such as sponsorship of the investigation or indirect benefits such as the provision of materials or facilities or the support of individuals such as provision of travel or accommodation expenses to attend conferences. Such disclosure should cover any situation in which the conflict of interest may, or may be perceived to, affect decision regarding other people.

The procedures should require disclosure to editors of journals, to the readers of published work, and to external bodies from which funds are sought.

Principal investigators have an obligation to disclose at the time of reporting, proposing research, or seeking approval from Ethics Committee or other regulatory authorities any conflict of interest which has a potential to influence the trial and its conduct.

Member of ethics committees must withdraw from the committee when discussion on their own projects are taken and must not use their membership on the committee to gain a favourable advantage

Individual members of ethics committees may also have a conflict of interest in accepting undue or excessive honoraria for their participation in for example, private ethics committees. Care must be taken to ensure financial and administrative independence of ethics committees so as to enable them to adequately fulfil their duties.

Footnotes Chapter 8

[14] Joint NH& MRC.AVCC Statement and Guidelines on Research Practice. Australia, 1990; Canadian Code of Ethical Conduct for Research Involving Humans, May 1997

9. Ethical Consideration For HIV/AIDS Clinical and Epidemiological Research - Contents

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9. ETHICAL CONSIDERATIONS FOR HIV/AIDS CLINICAL AND EPIDEMIOLOGICAL RESEARCH

This section emanated out of a series of consultations held by the Task Group on Ethical Guidelines for HIV research. While this document aims to provide broad ethical guidelines that address the current challenges posed by HIV/AIDS research, it is understood that new problems will continue to present themselves. For this reason this section will be continuously reviewed and revised when necessary. The particular ethical challenges posed by HIV vaccine research will be addressed in a subsequent Department of Health (DOH) guideline.

9.1 BACKGROUND

In recent years there has been an increase in HIV related clinical and epidemiological research. This has included advances in anti retroviral therapy, which has influenced the clinical course of HIV infection, reduced mother to child HIV transmission and HIV transmission following occupational exposure to HIV. There has also been an increase HIV vaccine research that is now an international priority. HIV related clinical research includes strategies to prevent HIV infection (i.e. vaginal microbicides) and to investigate medications that may increase the risk of HIV infection (i.e. long acting progestins). This research often necessitates determining the HIV status of individuals involved in clinical trials.

Clinical and epidemiological research involves complex ethical challenges. These include issues such as access to clinical trials, informed consent, use of medications after the completion of drug trials, drug toxicities, informed consent, long term side effects, the appropriateness of proposed research for South Africa, and the release and publication of the research results.

South Africa is a middle income country with severe economic disparities. The majority of the population is of a low socio-economic status. South Africa, however, is in many ways an ideal country for clinical and epidemiological HIV related research. It has a rapidly expanding HIV/AIDS epidemic which is favourable for research studies. Its well-developed infrastructure offers clinical and scientific expertise, academic institutions of good standing, good laboratory and clinical facilities and an industrial infrastructure, with high standards in communications and other relevant technologies. Information gained from clinical and epidemiological research could have critical implications for South Africa and globally.

This document attempts to address several ethical issues relating to HIV/AIDS clinical and epidemiological research in South Africa. There are also national and international vaccine initiatives in South Africa. This will stimulate the development of appropriate ethical considerations relating to vaccine research.

With many ethical issues there are not always clear right or wrong answers. There are however several universally accepted ethical principles. These principles should be applied within the context of South Africa and this document is intended to facilitate a more uniform approach to common ethical issues relating to HIV/AIDS related research.

9.2 SELECTED ISSUES RELATING TO HIV/AIDS CLINICAL AND EPIDEMIOLOGICAL RESEARCH

9.2.1 Research should be appropriate for South Africa

International research ethical guidelines, including those of the Council for International Organisations of Medical Sciences, emphasise the need for proposed research to undergo ethical and scientific review in both the initiating and host countries. This is to avoid exploitation of patients in the host country and be responsive to the needs of vulnerable communities. Vulnerable communities are defined by UNAIDS as having some or all of the following characteristics:

- Limited economic development;
- Inadequate protection of human rights and discrimination on the basis of HIV antibody status;
- Inadequate community/cultural experience with or understanding of scientific research;
- Limited availability of health care and treatment options; and,
- Limited ability of individuals in the community to provide informed consent.

As a result of past exploitation and oppression, South Africans are vulnerable to ethical abuses. Care and sensitivity should be applied to prevent exploitation of South Africa's disadvantaged community.

Research from developed countries, including Phase I and Phase II clinical trials, should not be conducted in South Africa merely because we can offer better research opportunities. Research conducted in South Africa should be relevant to the health needs of this country.

Research and clinical trials however should be conducted within various settings and applied to communities with different social and economic circumstances. Research projects being undertaken in South Africa should be carefully evaluated and examined as to its current and future relevancy. The science of HIV/AIDS is developing rapidly and proposed interventions, which may seem to be costly and inappropriate at present, may indeed become realistic options in the future.

9.2.2 Research Standards

Vulnerable communities are often characterised by sub optimal living conditions and poor access to health and social services. This should not lessen the need for high research and use of universally accepted ethical standards. It is imperative that good research and ethical standards be applied in vulnerable and non-vulnerable communities.

9.3 HIV RELATED DRUG TRIALS

HIV related clinical trials not only refer to anti-retroviral drugs but also to trials with medications such as immune modulators, and drugs for the treatment and prevention of HIV related opportunistic infections.

9.3.1 Access to HIV related medication

Drug trials are conducted to determine various outcomes such as efficacy, safety, impact on health status of the individual, possible short and long term side effects, survival benefits, quality of life, adherence to drugs regimens, compliance with therapy and comparisons with other therapeutic options.

While antiretroviral therapy is effective, it is expensive and not available in the South African public sector. Participation in drug trials is often the only way of gaining access to antiretroviral therapy. Drug trials should not be conducted solely because they facilitate access of drugs for some patients, although this may often provide very positive benefits to the individual.

The rationale for drug trials should be independently assessed and evaluated on its merits. Researchers must ensure that patients in drug trials provide informed consent and understand the implications of the trial. This includes the advantages and disadvantages of all drug regimens, and the potential limitations in taking medications only for the period of the drug trial.

Ethics committees should consider these advantages and disadvantages to the trial participants and the general community to determine whether such trials are appropriate and relevant in the South African context.

Patient autonomy needs to be respected. Endeavours to promote autonomy should be pursued through seeking opinions of representatives of vulnerable communities including persons living with HIV/AIDS.

9.3.2 Placebo controlled trials

Ethical guidelines that apply to controlled therapeutic trials are generally sufficient to protect the rights of HIV-infected persons. A special case involves the use of placebo after an intervention has been shown to be effective. The general principle is that the use of placebo in these circumstances is unethical. However with increasing disparities in health care between wealthy and poor countries, therapy that has been shown to be effective is often unaffordable in resource-poor settings. This is particularly true of therapeutic advances in HIV infection, which is a far bigger health care problem in poor countries in sub-Saharan Africa than it is in the industrialised countries. It may be justifiable to use placebo in communities that do not have access to interventions that are the standard care in resource-rich settings.

In order to reach the ethical principle outlined above, the balance between potential harms and benefits should be such that the potential benefits to the community would considerably outweigh the harm. This issue is controversial and there is no international consensus. Widespread consultation is advisable prior to embarking on such studies.

9.3.3 Adverse Drug Effects

Drug trials have the potential to cause short and long term ill effects. The patient information section of the informed consent document should specify what action is to be taken in the event that the study drug or drugs are withdrawn due to side effects. In such a situation appropriate therapy required to manage the adverse drug effects should be made available within the study framework at no cost to the patient, by referral to the local health service, or through the patient's medical insurance unless exceptions have been agreed upon by all parties.

9.3.4 Patient Management after Withdrawal from a Study

If a patient withdraws from a study for any reason, or where a study is completed, they should be advised about the ongoing management of their condition. Except in cases where therapeutic efficacy is demonstrated (see 9.3.5), ongoing therapy should be according to the local standard of care. Costs of this care should be borne by the local health service, the patient's medical insurance or the patient

themselves.

9.3.5 Access to Study Medications Following the Completion of Clinical Trials

Many patients who participate in HIV/AIDS treatment trials have no alternative access to drug therapy. Where a patient has a therapeutic response to a study drug, that patient should be offered ongoing treatment. In designing studies, consideration should be given to the costs of long term provision of study drugs and of clinical monitoring, including the costs of medical staff. The duration of drug therapy in a study should be clearly stated in the patient information section of the informed consent document.

9.4 HIV TESTING

HIV testing is frequently required in clinical and epidemiological research. These areas include:

- Epidemiological studies, e.g. sentinel surveillance on pregnant women;
- Observational studies, e.g. the effect of long acting progestins on the risk of HIV transmission in women;
- Drug trials, e.g. establish the efficacy and safety, etc; and,
- Vaccine trials.

HIV testing is a complex issue with important implications and consequences to the individual. Informing persons that they are HIV positive impacts on their quality of life and should be considered to be a major intervention.

Knowing one's HIV status may have important advantages and disadvantages:

Selected advantages may include:

- Availing oneself to health care and counselling for HIV which has many benefits;
- Preventing the transmission of the HIV to sexual partners;
- Informing one's partner so that he/she can also prevent the spread of HIV;
- Avoiding blood donations; and
- Preventing mother to child HIV transmission

Selected disadvantages may include:

- Mental stress, depression and despair;
- Stigmatisation;
- Discrimination; and
- Rejection by family, friends, sexual partners and / or spouse.

The advantages and disadvantages of HIV testing should be carefully considered and included in informed consent forms.

9.4.1 Confidential HIV Testing

In confidential HIV testing, the following criteria need to be met:-

- Adequate pre-test counselling;
- Informed consent. In the case of children informed consent must be obtained from the parent or lawful guardian, as well as from the child if sufficiently mature. Consent for HIV testing should form part of the consent document for research that requires HIV testing of an individual;
- Adequate post-testing counselling; and
- Referral to an accessible centre for ongoing psychosocial support and basic

medical care. The centre should provide care that conforms at least to the national standard of care for HIV prevention and treatment including the provision of condoms.

9.4.2 Unlinked Anonymous HIV testing

This form of HIV testing is done for surveillance purposes such as the national antenatal survey. It is considered ethically acceptable to do anonymous unlinked testing without consent if the following criteria are met:

- Blood is routinely collected for a reason other than HIV testing;
- After routine testing personal identifiers are removed;
- Leftover blood or blood products are then used for HIV testing; and,
- No other non-routine interventions (including questionnaires) may be done.

Ideally, confidential HIV testing should be available to individuals in the target population where unlinked HIV testing is conducted. Referring individuals to voluntary counselling and testing centres should be considered.

9.4.3 Linked Anonymous HIV testing

In linked anonymous testing the HIV result is linked to a patient's other clinical data, but this is done without being able to identify the patient who remains anonymous. An independent person randomly assigns code numbers to patients' serum prior to HIV testing. The patients' identities are then removed from database and the order of patients is then changed. The HIV result is added to the database and "linked" to the other data obtained before being returned to the investigators. This form of testing is best suited to research where HIV infection is a major confounder and not when HIV infection is the endpoint. Patients should provide informed consent to linked anonymous testing and be offered confidential HIV testing (see 9.4.1).

In unlinked anonymous and linked anonymous HIV testing, researchers should not be able to directly or indirectly identify HIV test results of individuals.

9.5 POPULATION BASED STUDIES TO PREVENT HIV TRANSMISSION

These are studies designed to assess the impact of an existing or proposed intervention on the transmission of HIV in a particular population. Examples include studies to determine the impact of improved STD care in a community on the incidence of HIV; the effect of long term use of contraceptives on the risk of acquiring HIV infection, post sexual abuse antiretroviral prophylaxis, or placebo controlled mother to child transmission.

Observational research studies may not provide immediate personal benefits and usually requires large numbers of participants. Such studies require active community participation in both the design and the monitoring of this type of study if the intervention is to be applied to a population. Consent of community representatives is not a substitute for individual consent.

If an intervention has been shown to effectively reduce HIV transmission it should not be withheld from research participants. All subjects must be given information and the means to prevent HIV transmission by means of practising safer sex and effective treatment for sexually transmitted diseases. Any treatment offered should conform at least to the local standard of care.

9.6 INFORMED CONSENT AND INCENTIVES

Informed consent may be difficult to achieve, especially when engaging people from disadvantaged and vulnerable communities where literacy and education opportunities are inadequate and where there are language barriers. However, every effort must be carried out to achieve informed consent.

Incentives for patients to submit themselves for research purposes need careful consideration. Incentives should not be so excessive so as unfairly influence the patients to submit themselves to the trial. Incentives such as financial, transport, and food should be fair and reasonable without 'making the patient an offer they cannot refuse' and thereby influence the patient to overlook other important consideration.

9.7. RESEARCHER ISSUES

9.7.1 Incentives

Pharmaceutical companies doing research on their products frequently offer researchers incentives. Researchers should guard against these 'incentives' promoting excessive allegiance with a pharmaceutical company, which may adversely affect their objectivity and neutrality. Researchers and members of ethical committees should disclose their financial interests relating to proposed research projects.

9.7.2 Releasing and publishing research results

In recent years some investigators have released preliminary research data prematurely to the press with serious and negative consequences. This may result in the release of sensational, inaccurate, misleading and irresponsible information on HIV/AIDS. Unfounded claims may mislead the public and create unrealistic expectations. In order not to create unrealistic or misleading expectations the following must be carefully considered:

- Researchers should not communicate the results of clinical trials to the public without first subjecting the study to peer review and to the normal rigorous scientific scrutiny needed for therapeutic and vaccine trials.
- Phase I and II trials should be published in scientifically refereed journals or presented to scientific forums where the results can be openly viewed and scrutinised. These results should not be released to the mass media before peer review because they may be misinterpreted, misunderstood, sensationalised and result in serious public misunderstanding.
- Important findings, which need to be urgently released, should be done via the 'fast track' system employed by most reputable scientific journals. Most medical journals have now developed this system to fast track review and publish important research findings.

9.7.3 Implementing Research Findings

Research, which has direct public health implications, such as vaccine trials, require wide consultation. This should include discussions with the South African Department of Health and the Medical Research Council so that implementation of study results can be addressed at an early stage.

9.7.4 Research ethics committees and field support

Proposals for clinical and epidemiological research should be submitted to relevant local ethics committees or to the South African Medicines and Medical Devices Regulatory Authority for approval.

Principle researchers or investigators must provide adequate supervision to ensure that ethical considerations are met in a full and proper manner by their delegated staff.

9.8 HIV VACCINE RESEARCH

There are currently a variety of international and national vaccine initiatives in South Africa. This research is highly specialised and it raises many ethical issues. This document will not address the range of issues that are being addressed by the appropriate vaccine research groups. Some

of the important ethical considerations include:

- The implications of wide spread HIV testing on high risk populations;
- The impact of local HIV prevention initiatives on research outcomes;
- The possible influence of the vaccine candidates to offer a disincentive for people to take necessary precautions to prevent HIV transmission;
- The implications of 'false positive' HIV tests in patients who agree to vaccine trials; and,
- The appropriateness of the vaccine clade to the local population.

Vaccine research should be done in consultation with the national and international initiatives.

9.9 INVOLVEMENT OF PEOPLE LIVING WITH HIV/AIDS (PWAS)

The many tensions, dilemmas and ethical consideration surrounding HIV/AIDS related research necessitates a wide consultative process. PWAs are critical to this process and should form part of the consultation from the very early stages of the research process.

9.10 SPECIAL CONSIDERATIONS TO SPECIFIC SUBGROUPS OF THE SOCIETY

In addition to vulnerable communities, there are vulnerable populations that require special consideration. These include women, prisoners, and children. Women should be appropriately represented as research participants unless there is a clear and compelling rationale that such inclusion is inappropriate.

In research involving prisoners, researchers should ensure that voluntary informed consent is provided. Ethics committees considering research proposals involving prisoners should consider the inclusion of prisoners or prison representatives on such reviews.

In investigations regarding pregnant women, researchers should not limit normal standards of care nor inappropriately affect decisions concerning pregnancy termination.

APPENDIX A

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 subjects 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, subjects 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 subject 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 subjects 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.

<p>WORLD ASSOCIATION DECLARATION OF HELSINKI</p> <p>Ethical Principles For Medical Research Involving Human Subjects</p>
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Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principle to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethics standards that promote respect for all human beings and protect their health and rights. Some research population is vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for

those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirements should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subject must conform to general accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animal used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical human research involving subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subject should be preceded by careful assessment of predictable risk and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research project involving human subjects unless they are confident that the risk involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigations if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the result of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must be always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of every patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In research of human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may

- consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mental incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
 25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
 26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristics of the research population. The specific reason for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from individual or a legally authorized surrogate.
 27. Both authors and publishers have ethical obligation. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principle laid down in this Declaration should not be acceptable for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX B

CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)¹

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

1. General Information

- Protocol title, protocol identifying number, and date. Any amendment(s).
- Should also bear the amendment number(s) and date(s).
- Name and address of the sponsor and monitor (if other than the sponsor).
- Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
- Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.
- Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
- Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
- Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department (s) and/or institutions involved in the trial.
- Written curriculum vitae of principal investigator, co-investigators and other persons designated by the principal investigator to be responsible for some aspects of the study.

2. Background Information

- Name and description of the investigational product(s).
- A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
- Summary of the known and potential risks and benefits, if any, to human subjects.
- Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
- A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
- Description of the population to be studied.
- References to literature and data that are relevant to the trial, and that provide background for the trial.²

3. Trial Objectives and Purpose

- A detailed description of the objectives and the purpose of the trial.

4. Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

- A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
- A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
- A description of the measures taken to minimize/avoid bias, including:
 - a. Randomization.
 - b. Blinding.
- A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).
- The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
- A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.
- Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
- Maintenance of trial treatment randomization codes and procedures for breaking codes.
- The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

5. Selection and Withdrawal of Subjects

- Subject inclusion criteria.
- Subject exclusion criteria.
- Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
 - a. When and how to withdraw subjects from the trial/investigational product treatment.
 - b. The type and timing of the data to be collected for withdrawn subjects.
 - c. Whether and how subjects are to be replaced.
 - d. The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6. Treatment of Subjects

- The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.
- Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

- Procedures for monitoring subject compliance.

7. **Assessment of Efficacy**

- Specification of the efficacy parameters.
- Methods and timing for assessing, recording, and analysing of efficacy parameters.

8. **Assessment of Safety**

- Specification of safety parameters.
- The methods and timing for assessing, recording, and analysing safety parameters.
- Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.
- The type and duration of the follow-up of subjects after adverse events.
- Procedures for unmasking the identity of treatment.

9. **Statistics**

- A description of the statistical methods to be employed, including timing of any planned interim analysis (ses).
- The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified.
- Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
- the level of significance to be used.
- Criteria for the termination of the trial.
- Procedure for accounting for missing, unused, and spurious data.
- Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
- The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, valuable subjects).

10. **Direct Access to Source Data/Documents**

- The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, ethics committee review, and regulatory inspection(s), providing direct access to source data/documents.

11. **Quality Control and Quality Assurance**

12. **Ethics**

- Description of ethical considerations relating to the trial.

13. Data Handling and Record Keeping

14. Financing and Insurance

- Financing and insurance if not addressed in a separate agreement.

15. Publication Policy

- Publication policy, if not addressed in a separate agreement.

Footnote

[1] SOURCE: ICH Guidelines for Good Clinical Practice

[2] Systematic Review: The research protocol should demonstrate knowledge of relevant literature and wherever possible be based on prior laboratory and animal experiments. Researchers do not always take into proper account the results of existing research when planning new clinical trials. This constitutes unethical practice for several reasons. Firstly, if existing evidence is available that an active form of care is better than placebo, further placebo controlled research denies some patients effective treatment. Such research should only be considered where there is a need to evaluate additional important outcomes, including adverse effects. Secondly, failing to take into account evidence that a treatment is ineffective, or that it does more harm than good, inevitably exposes patients to inconvenience or unnecessary risk. Thirdly, conducting trials that address previously answered questions wastes limited resources.

Systematic review has evolved over the past decade as a rigorous methodology for synthesising the results of primary research. The process involves identification, appraisal and integration of the findings of published and unpublished studies, with the aim of drawing conclusions from the totality of relevant evidence. All ethics committees must therefore:

- Insist on a well-conducted systematic review of relevant existing research as a precondition for approving new research. The review should provide convincing evidence that proposed research is necessary, that it will not expose patients to unacceptable risks or practices, and that it will not withhold care that is known to be effective.
 - Require that researchers make available to potential trial participants a summary of the finding of the systematic review before requesting their consent. Both the possible benefits and the risks of treatment should be clearly stated.
 - Help to minimise bias resulting from non-publication of negative studies by (a) ensuring registration of clinical trials at inception and (b) requiring a written commitment from investigators to publish the results of trials.
-

APPENDIX C

DETAILS OF AN MCC INSPECTION

The inspection may involve;

1. a comparison of the practices and procedures of the clinical investigator with the commitments made in the application to conduct a clinical trial and/or
2. a comparison of the data submitted to the sponsor and regulatory authority with the source data.

THE INSPECTION

PRE-INSPECTION CONTACT

Where appropriate, appointments for inspection of an investigational site should be made telephonically. The Medical Director of the relevant pharmaceutical company also need to be contacted, as the clinical research associate (CRA) of the company responsible for the monitoring of the specific study needs to be present during the inspection.

The MCC official should, however, keep the time span between initial contact and actual inspection as short as possible. What appears to be undue delay of the inspection on the part of the clinical investigator needs to be investigated.

PRE- INSPECTION MEETING

The purpose of this meeting is for the MCC official(s) to explain the purpose of the inspection, i.e routine or for -cause, and to establish whether the investigator has fulfilled his/her GCP responsibilities. The latter includes:

- Whether the investigator is thoroughly familiar with the properties of the investigational medical product(s) as described in the investigator's brochure.
- to ensure that he/she has sufficient time to conduct and complete the clinical study, has adequate staff and appropriate facilities (including laboratories) available for the duration of the study, and to ensure that other studies do not divert essential subjects/patients or facilities away from the study in hand.
- the investigator needs to provide retrospective data on numbers of subjects/patients who would have satisfied the proposed entrance criteria during preceding time periods in order to assure an adequate recruitment rate for the study.
- the investigator needs to provide an up-to-date curriculum vitae.
- to establish whether the investigator has studied the protocol and whether the assisting personnel have been adequately informed of their responsibilities.
- to determine if Ethics Committee approval has been obtained.
- to determine in what manner the investigational products are handled and stored, and that investigational products are dispensed to study subject/patient in accordance with the protocol and that any unused products are returned to the Sponsor. Reconciliation of trial medication must be provided.
- to ensure that the confidentiality of all information about subject/patients is respected (by all persons involved). to ensure that the investigator observes the following points particularly related to patient care:
 - if appropriate, fully functional resuscitation equipment should be immediately available in case of emergency.
 - the Investigator is medically responsible for those subjects/patients who are under his/her care for the duration of the study and must ensure that appropriate medical care is maintained after the study.
 - clinical significant abnormal laboratory values or clinical observations must be followed up after completion of the study.

THE INSPECTION

SITE MASTER FILE

The following original documents or certified copies thereof must be available at the investigational site:

- Investigator's Brochure
- Protocol, including all amendment
- MCC approval for original application and all the amendments
- Ethics Committee approval, including approval of all amendments
- Trial subject informed consent
- Investigator's CV
- CRFs

INSPECTION PROCEDURES

This part identifies the nature of the information that must be obtained during each inspection to determine if the clinical investigator is meeting his/her obligation as trialist. This outline provides only the minimal scope of the inspection and the MCC official should extend the inspection as the facts involve. The inspections conducted should be sufficient in scope to determine compliance with GCP. The MCC official should not attempt to evaluate scientific data during the inspection, but only verify documentation and validate data.

- The protocol, included and amendments must be signed by the investigator.
- Documentation Ethics Committee and MCC approvals must be verified.
- Signed informed consent documents must be validated. The signatures need to be checked against evidence on patient files. Date of consent must be prior to date of initiation of trial. If oral consent was obtained, it must be determined whether this was recorded in the subject's medical records. A copy of the information presented orally must be obtained.
- Subject records must be verified.
- The condition, organisation, completeness and legibility of the investigator's raw data files need to be described.
- It needs to be determined whether there is adequate documentation to assure that all audited subjects did exist and were alive and available for the duration of their stated participation in the study.
- The raw data in the clinical investigator's records needs to be compared with the completed case reports.
- The following needs to be determined:
 - whether the number and type of subjects entered into the study were confined to the protocol limitations.
 - whether the criteria (e.g age, sex, reproductive potential, disease condition) for exclusion of subjects from the study, as specified in the protocol were followed

- observations, information, and data condition of the subject at the time the subject entered into the trial.
 - observations and data on the condition of the subject throughout participation in the investigation, including results of lab tests, development of unrelated illness and other factors which might alter the effects of the test article.
 - Records of exposure of the subject to the test article.
 - Whether clinical laboratory testing (including ECGs X-rays and other special investigations), as noted in the case reports, can't be evaluated by the presence of completed laboratory reports in the source documents.
- The occurrence of adverse reactions must be determined. The reporting of these events to MCC and the Ethics Committee must be documented.
 - All persons obtaining raw data or involved in the collection or analysis of such data need to be identified.
 - It needs to be determined whether all products, and the reasons therefore were reported to the Company.

TRIAL MEDICATION

- Accounting procedures for the test and comparator drugs must be determined.
- Dates and quantity of trial medication dispensed as well as the recipients must be available as well as corroboration by raw data notations.
- The blinding of medication, if appropriate, must be validated to ensure protection of the study from bias.
- It needs to be determined whether distribution of the article was limited to those persons under the investigator's direct supervision.
- The storage area may be inspected.
- It needs to be determined whether the test article is a controlled substance and whether it is securely locked.
- Access to the controlled substance must be restricted to the investigator and the responsible pharmacist.

COMPUTER ELECTRONIC DATA SYSTEMS

If electronic data systems are involved in gathering data, storing data, or transmitting data to the sponsor, these need to be identified and their capabilities established.

The following are important:

- What is the source of data entered into the computer?
- Who enters data ?
- When

- Who has access to computer? Security codes?
- How are data previously entered changed? Audit trail? By whom?
- How are data submitted to sponsor? (hard disk, floppy disk, fax, modern network, mail, messenger)
- How are errors, omissions, etc., in the data received corrected and how are they documented?

POST-INSPECTION MEETING

At this meeting the MCC official(s) will convey the findings of the inspection to the investigator and the representative of the pharmaceutical company or contract research organisation. The matters discussed at this meeting will be in line with the report written by the official.

Important matters include:

- When significant violations of GCF are suspected, reports must contain sufficient narrative and accompanying documentation to support the findings. These findings also need to be presented to MCC.
- When it is apparent that the study has been conducted in substantial compliance with the guidelines, an abbreviated report may be submitted.

The following is a guideline as to what should be included in an abbreviated report:

1. The comparison of raw data recorded on the case report forms to that of the source data, including the number of records compared and what was compared (patient charts, hospital records, lab slips and etc.)
2. There should be a statement about the trial medication accountability records was not sufficient to reconcile the amount of medication received, dispensed and/or returned.
3. There should be a statement about protocol adherence, which should be characterized and quantified.
4. There should be a statement about the obtaining of informed consent from each patient
5. There should be a statement identifying the specific individual responsible for each significant aspect of the study (who saw the patient, who administered the test medication, etc.).
6. There should be a statement on follow-up of adverse experiences (including death) if any occurred.
7. If deficiencies are found during the inspection in any of these or in any of the areas it needs to be explained and documentation attached as exhibits.
8. A copy of the consent form and protocol actually used needs to be attached.

It is important to note that the above deals with an abbreviated report, not an abbreviated inspection.

All clinical investigator audits conducted for cause must have full reporting.

A for-cause inspection may be the result of prior knowledge or suspicion of alleged violations of the act and/or guidelines. A for-cause inspection may concentrate the data audit on specific

areas of the study or may expand the data review to cover multiple studies. This inspection may also result when a study is of singular importance to the approval of registration of a medicine, i.e one of two adequate and well controlled studies

APPENDIX D

DRAFT MCC CLINICAL TRIAL EVALUATION CHECK-LIST

1.1 Previous research relating to safety and potential benefit of intervention

- Do the results of laboratory and animal studies provide sufficient indication of the potential benefits and safety of the trial treatments in humans?
- Has appropriate information been supplied regarding the kinetics and dynamics of the trial treatments?
- Is this trial necessary? Do the investigators refer to a rigorous, preferably systematic review, of all previous trials that show the proposed trial would contribute further to existing knowledge?

1.2 Trial Methods

- Are the objectives of the trial sufficient described?
- Re the selection criteria for entry to the trial appropriate?
- Is the source of participants sufficiently described/
- Are the treatments well defined?
- What method of randomisation will be used?
- How will allocation to treatment groups be concealed?
- Will participants, providers of care or assessors of outcome be blinded?
- Are the outcome measures appropriate?
- Will both benefits and harms of treatment be assessed?
- Will both prognostic factors be considered?
- Is there an acceptable calculation of required sample size?
- Is the duration of post-treatment follow-up stated?

1.3 Ethical Issues

- Will the trial be supervised by a clinically competent, medically qualified person?
- Have the specific roles of each investigator been stated? Are these roles commensurate with the qualifications and experience of the investigators?
- Has the remuneration to be received by the investigators and /or participants been disclosed?

- Have all the investigation sites been listed? Do the sites have sufficient capability to carry out the study?
 - Have suitable arrangements been made to monitor protocol compliance, drug dispensing, adverse effects and data processing?
 - Have suitable arrangements been made for interim analyses and how will stopping rules be applied?
 - Is there a clear statement confirming that the applicant has satisfactorily addressed insurance and indemnity issues?
 - Do the investigation plan to obtain informed consent (in writing if possible) from study participants? Will all potential participants be adequately informed about the aims and methods of the study; the anticipated benefits, potential hazards and inconveniences associated with being in the study; and their rights to withdrawal from the study without prejudicing further treatment?
 - Have the investigators confirmed in writing that adequate reports of the research will be made publicly accessible within a reasonable period of time?
 - Has the trial protocol been approved by an appropriate ethics committee of the participating institution?
-

APPENDIX E

DISCLOSURE OF CONFLICTING INTERESTS³

1. A member of the Board or of the staff or of any committee of the Authority, may not vote at, attend or in any other manner participate in the proceedings of any meeting or hearing of the Board or any committee of the Authority if:
 - in relation to an application for the registration of a medicine, complementary medicine, veterinary medicine, clinical trial or device, that member or that member's immediate family member or business partner is a director, member or business partner of or has an interest in the business of the applicant of any person who made representations in relation to the application; or
 - in relation to any matter before the Authority, has any interest which precludes or may be perceived as to preclude that member from performing that member's functions as a member of the Authority in fair, unbiased and proper manner.
2. For the purpose of this section, "interest" includes, but is not limited to, any consultancy, paid or unpaid, any research grant from which the member directly or indirectly benefits, or any equity holding or any executive or non-executive directorship or any other payment or benefit in kind.
3. If at any stage during the course of any proceedings of the Board or committee of the Authority has an interest contemplated in subsection (1), that member:
 - a. must forthwith and fully disclose the nature of that member's interest and leave the meeting or hearing in question so as to enable the remaining members of the Board or any committee of the Authority to discuss the matter and determine whether that member should be preclude from participating in such proceedings by reason of a conflict of interests, and
 - b. such disclosure and the decision taken by the remaining members of the Board or any committee of the Authority regarding such determination, must be recorded in the minutes of the proceedings in question.

Footnote

[3] Office of the President (1998) *No. 132 of 1998: South African Medicines and Medical Devices Regulatory Authority Act, 1998*. Gazette Number: 19615, Part 1 of 2. Volume 402. Notice Number: 1634. Date: 18 December 1998

APPENDIX F

1. GLOSSARY ⁴

1.1 Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3 Amendment (to the protocol)

See Protocol Amendment.

1.4 Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

1.5 Approval (in relation to Institutional Review Boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.6 Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.7 Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

1.8 Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

1.9 Audit Trail

Documentation that allows reconstruction of the course of events.

1.10 Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11 Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

1.12 Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13 Clinical Trial/Study Report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

1.14 Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

1.15 Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

1.16 Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

1.17 Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18 Coordinating Committee

A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

1.19 Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

1.20 Contract Research Organization (CRO)

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

1.21 Direct Access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

1.22 Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23 Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

1.24 Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25 Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26 Impartial Witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27 Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as

described in this guideline.

1.28 Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

1.29 Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30 Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31 Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32 Interim Clinical Trial/Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33 Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.34 Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

1.35 Investigator / Institution

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

1.36 Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see Investigator's Brochure).

1.37 Legally Acceptable Representative

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.38 Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.39 Monitoring Report

A written report from the monitor to the sponsor after each site visit and/or other trial related communication according to the sponsor's SOPs.

1.40 Multicentre 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.

1.41 Nonclinical Study

Biomedical studies not performed on human subjects.

1.42 Opinion (in relation to Independent Ethics Committee)

The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

1.43 Original Medical Record

See Source Documents.

1.44 Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

1.45 Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

1.46 Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

1.47 Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48 Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49 Regulatory Authorities

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.51 Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52 Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

1.53 Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54 Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.55 Standard Operating Procedures (SOPs)

Detailed written instructions to achieve uniformity of the performance of a specific function.

1.56 Subinvestigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

1.57 Subject/Trial Subject (Participant)

An individual who participates in a clinical trial, either as a recipient of the investigational product (s) or as a control. WHO (2000) also defines a research participant " An individual who participate in the a biomedical research project, either as direct recipient of an intervention (e.g., study product or invasive procedure) as a control, through observation. The individual may be healthy person who volunteers to participate in the research, or a person with a condition unrelated to research carried out who volunteers to participate, or a person (usually a patient) whose condition is relevant to the use of the study product or question being investigated". (Note: The Guidelines for GCP in the conduct of Trials in Human Participants in SA use the term "participant" to refer to "subject or trial subject").

1.58 Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

1.59 Trial Site

The location(s) where trial-related activities are actually conducted.

1.60 Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.61 Vulnerable Subjects

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 subjects 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.

1.62 Well-being (of the trial subjects)

The physical and mental integrity of the subjects participating in a clinical trial.

Footnote

[4] SOURCE: ICH Guidelines for Good Clinical Practice

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