

# **SOUTH AFRICAN GOOD CLINICAL PRACTICE GUIDELINES**

**SECOND EDITION**

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## PREAMBLE

This is the second edition of the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa following those published in 2000. They have been revised by a working group convened by the Director-General of the Department of Health that principally included representatives from the Department of Health, the Medicines Control Council and the Interim Ministerial Committee on Ethics in Health Research.

The Guidelines are addressed to investigators including ethics review committees, pharmaceutical manufacturers and other sponsors of research, drug regulatory authorities, the general public and all those who have an interest in clinical trials research in South Africa.

By providing a basis both for the scientific and ethical integrity of research involving human subjects and for generating valid observations and sound documentation of the findings, these Guidelines not only serve the interests of the parties actively involved in the research process, but protect the rights and safety of participants, including patients, and ensure that the investigations are directed at the advancement of public health objectives.

These Guidelines will support the regulatory requirements of the Medicines Control Council and regulations related to Health Research in the National Health Act. It is therefore critical that research ethics committees, researchers, trial participants, principal investigators of trials and sponsors use these guidelines so as to ensure a standardised and ethical approach to clinical trial activities in South Africa. The guidelines are also applicable to both academic and contract clinical research.

The Guidelines are intended to be applied during all stages of drug development -both prior to and subsequent to product registration and marketing, and they are also applicable, in whole or in part, to biomedical research in general. They should also provide a resource for editors to determine the acceptability of reported research for publication and specifically, on any study that could influence the use or the terms of registration of a pharmaceutical product. Not least, they provide an educational tool that should become familiar to everyone engaged in biomedical research and, in particular, to every newly trained clinician.



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## ACKNOWLEDGEMENTS

These national guidelines have been developed to promote good practice in the conduct of clinical trials in South Africa. The revision process of these guidelines started in 2005 through a number of consultations with regulatory authorities, the pharmaceutical industry, Community Advisory Boards and the Department of Health. A smaller team was convened to compile and adjudicate contributions from respectable stakeholders.

The team members 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; in particular Dr L E Makubalo (Chief Director), Ms P Netshidzivhani (Director) Ms M Ratsaka-Mothokoa and Mr K Hlongwa of the National Department of Health.

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## **1. INTRODUCTION**

The value of carefully constructed 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 world class expertise in clinical trial research, modern health care facilities, a significant burden of disease, and a stable political environment. 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 participants to investigate emerging and re-emerging diseases lit up by urban deprivation.

It is estimated that the clinical trial industry in South Africa has grown by as much as 40% from 1997-1998<sup>1</sup> and yielded an estimated total budget of R826 million during 2000.<sup>2</sup> The value of the clinical trial industry is unquestionable. It is both a major source of foreign revenue and employment for the country. Moreover undertaking clinical trials in South Africa helps to retain and increase valuable research expertise.

Achievement of scientific goals however must be secondary to the protection of research participants. As such, the outcomes of clinical trials are only acceptable when conducted in an ethical way. It is widely accepted that all research participants are entitled to minimum guarantees that are transnational and non-negotiable.<sup>3 4</sup> These entitlements can be realized through in-country systems and structures that support and promote good clinical practice. An important component of these systems and structures are national ethics guidelines for good clinical practice.

In recognition of this a working group convened by the Director General of Health developed Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants.

### **1.1 WHY GUIDELINES?**

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 and 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 clinical trial data are credible.

### **1.2 PRINCIPLES**

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.

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<sup>1</sup> Christley (1998)

<sup>2</sup> Joffe (2000)

<sup>3</sup> Studdert DM and Brennan T A (1998) Clinical trials in developing countries: scientific and ethical issues. *Medical Journal of Australia*, 169:545-548

<sup>4</sup> Minimum guarantees are: The study must have a valid scientific design and be performed by qualified persons; It must strike a reasonable balance between the predictable risks and foreseeable benefits to the subjects or others, with the proviso that the subjects' interests should never be subordinate to those of science and society; All study subjects must consent to participate, a decision that must be made without duress or coercion and only after details of the study are provided; and in multi-country studies/sites the research must hold the promise of direct, tangible and significant benefit to the host country, if not the study subjects themselves.

These include the following:

- Respect for the dignity of 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.

**1.2.1. Study Rationale and Motivation:** A study rationale and motivation which does not ask relevant and important questions is unethical. The study rationale should demonstrate that the study question under consideration has not been substantially answered and that adequate systematic review of the subject under discussion was done. Relevant and important questions should also be problems that significantly affect local and regional populations.

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.<sup>5</sup>

The findings of the proposed study should be translatable into mechanisms for improving the health status of South Africans. Solutions should have the potential for implementation.

**1.2.2 Study Designs:** Appropriate study designs are critical in contributing to answering scientific questions. The study 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 be provided.

The social context of a proposed research population that creates conditions for possible exploitation or increased vulnerability among potential research participants should be assessed, where this is relevant. Steps must be taken to overcome these conditions, and to promote and protect the dignity, safety and welfare of participants. The vulnerability factors and steps that will be taken to offset these should be addressed in the study design and clearly outlined in the research protocol.<sup>6</sup> It is imperative that sound study designs, and use of universally accepted ethical standards are applied in both vulnerable and non-vulnerable communities.

The design of the study should in no way prejudice the ongoing treatment and care of patients, nor should it in anyway undermine or confuse patients with respect to the best available local standard treatment practices and national policy approaches.<sup>7</sup> If these are not ensured, then the design is unethical.

**1.2.3 Investigator Competence:** The Principal Investigator's (and other investigators') competence is assessed by two major parameters: technical and humanistic. Technical competence which includes research competence is assessed by education, knowledge, certification and experience such that the investigator is able to assume responsibility for the proper conduct of a trial, should meet all the qualifications specified by applicable

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<sup>5</sup> E.g the science of HIV and 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.

<sup>6</sup> For a more detailed discussion on research in vulnerable communities see section 2.3.11.

<sup>7</sup> 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

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 and / or regulatory authority(ies). 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 for each site must be a South African-based scientist (resident in South Africa).

**1.2.4 Balance of Harm and Benefit:** A risk benefit analysis of the study should precede the conduct of the research itself. The 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 risk.

**1.2.5 Transparency:** Clinical trialists have an ethical obligation to honestly report a trial's existence and findings. Publication bias among other things often serves as a barrier to this and can distort the body of evidence available for clinical decision making. The South African Department of Health in partnership with academia, industry and other key stakeholders, has established the South African National Clinical Trial Register (SANCTR) – a central publicly accessible clinical trial register.

Benefits of the SANCTR are numerous. It serves to: promote collaboration among researchers, the private sector and the community through the sharing of research information; assist people to identify clinical trials they can participate in; decrease publication bias; reduce duplication of research efforts; promote best use of limited research resources; and contribute to global efforts to reduce/eliminate disease (while preserving the confidentiality of commercially valuable information regarding the medicine during the development stage). Sponsors of trials conducted in South Africa are required to register their trials on the SANCTR at [www.saclinicaltrials.gov.za](http://www.saclinicaltrials.gov.za). Where there is no sponsor, it is the responsibility of the Principal Investigator to register the trial.

**1.2.6 Privacy:** Participants' right to privacy must be protected at all costs. This is maintained via the use of appropriate precautions regarding participant identifiers. This will also include electronic/computerised records and access thereof of such information.

**1.2.7 Ethical Review:**<sup>8</sup> Ethical review 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. The following bodies are involved in ethical review in South Africa:

- **Research Ethics Committees:** Research Ethics Committees are usually made up of lawyers, medical practitioners, bio-ethicists and community representatives. All clinical trials conducted in South Africa must undergo ethical review by an accredited ethics committee.
- **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.

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<sup>8</sup> For more information on ethical review refer to Department of Health *Ethics in Health Research: Principles, Structures and Process, 2004*. ISBN: 1-920031-04-9, [www.doh.gov.za](http://www.doh.gov.za)

- The Medicines Control Council (MCC): Whilst the MCC is not an ethical review committee it is responsible for reviewing the study design, and in so doing reviews all significant ethical questions.
- The National Health Research Ethics Council (NHREC): The NHREC is a central body which advises the Department of Health on the management of health research ethics in South Africa. Among other things it is responsible for overseeing and accrediting South African ethics committees.

**1.2.8 Informed Consent:** Informed consent is an essential component of ethical research. 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.

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.

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 of choice. 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.

**1.2.9 Safety Monitoring:** Safety monitoring of participants during and for defined periods after a clinical trial is an ethical requirement. This involves the prevention, appropriate monitoring, prompt reporting and appropriate management of serious adverse events.

**1.2.10 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 of such studies are appropriate for the local setting and that particular modifications are made to the local study when required e.g. inclusion/exclusion criteria. Special attention should also be paid to the sampling strategy when reviewing multi-centred clinical trials.

Furthermore, 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.

Other issues in multi-centre studies include the appropriateness of incentives packages to trial participants and remuneration packages for investigators. For further discussion on multi-centre studies refer to Section 7.

### 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, particularly research involving experimental study designs. These guidelines have been guided by and based on the following documents:

- ICH Guideline for Good Clinical Practice, ICH Harmonised Tripartite Guideline<sup>9</sup> (Appendix A)
- Declaration of Helsinki (Appendix A)
- 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
- 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 Institutes 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

Regulations established in terms of section 90 (s) of the National Health Act, Act No, 61 of 2003 enforces these guidelines. 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 apply to a particular issue or activity of the clinical trial, the legal requirement will always apply.

### 1.5 REGULATORY AUTHORITIES 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 Medicines Regulatory Authority (MRA)/Medicines Control Council:** 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 (GCP), the MCC can terminate the trial. The Medicines Regulatory Authority is secretariat to the MCC.

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<sup>9</sup> Written permission to use the ICH guidelines on a non-commercial basis was given by the ICH secretariat.

- 1.5.2 South African National Clinical Trial Register (SANCTR)/Department of Health:** Sponsors are required to register all South African based trials on the South African Clinical Trial Register (SANCTR) managed by the Department of Health. If there is no sponsor, then it is the responsibility of the PI to register the trial. Once registered, the trial will be issued a unique study number within two working days of the application being received by the Department of Health. Trials should not commence without this number. Section 1.6 refers.
- 1.5.3 The National Health Research Ethics Council (NHREC):** This body will have overall responsibility to promote, ensure and monitor compliance by research ethics committees in South Africa with relevant legislation, regulations and guidelines. In so doing, the National Health Research Ethics Council will accredit and audit the performance of research ethics committees. It has been established under the National Health Act, Act No. 61 of 2003. This body reports directly to the Minister of Health and is provided with secretariat support from the research directorate of the Department of Health.
- 1.5.4 Research Ethics Committees (REC):** The main responsibility of Research Ethics Committees (REC) in South Africa is to ensure the protection of, and respect 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. (See Section 8 for more information on Research Ethics Committees).
- 1.5.5 The Principal Investigator (PI):** The principal investigator is a South African 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. See Appendix F for definitions of investigator/sub-investigator.
- 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 the 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, local and other regulatory authority(ies) 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.

**1.5.9 The Inspector:** The inspector is a qualified employee of local and international regulatory authority(ies) whose responsibility is to conduct announced or unannounced inspection visits at clinical trial sites/sponsors/CROs/bioequivalence facilities and research ethics committees as required/instructed by the regulatory authority(ies). Most inspectorate visits will be prearranged but some will not especially where there is suspected serious breaches of the GCP or malpractices. (See Appendix C for details of a MCC inspection).

## 1.6 CLINICAL TRIAL APPROVAL IN SOUTH AFRICA

The following steps must be undertaken before a clinical trial can be conducted in South Africa:

- **National Regulatory Authority Approval:** A sponsor/principal investigator (PI) must apply to the MCC for approval to conduct a trial for a non-registered drug or a registered drug for new indications;
- **Research Ethics Committee Approval:** All clinical trials to be conducted in South Africa must apply for and receive ethical approval from an accredited research ethics committee based in South Africa (this is also applicable to multi-national trials);
- **Recording on South African National Clinical Trials Register (SANCTR):** Once the trial has obtained ethical approval, trial information must be forwarded to the Department of Health where the trial is allocated a unique SANCTR number – it is the responsibility of the sponsor/principal investigator to ensure that information is sent to the Department of Health. The number will be generated within two working days of the application having been received. Only once this number is received by the sponsor/PI can the trial begin.<sup>10</sup>

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<sup>10</sup> For more information on SANCTR go to <http://www.doh.gov.za> and use the clinical trials register link on the Department of Health home page

## **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 these Guidelines, the Declaration of Helsinki, ICH Guidelines for Good Clinical Practice and the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Ethics in Health Research: Principles, Structures and Processes, and the Guidelines on Ethics for Medical Research: HIV Preventive Vaccine Research.

### **2.2 ETHICAL REVIEW**

All medical research involving human participants must undergo an independent ethical review. The Research Ethics Committee which undertakes the review must be accredited by the National Health Research Ethics Council.<sup>11</sup> In the evaluation of clinical trial protocols or study applications, the Research Ethics Committee must ensure that participants are protected in accordance with international standards and guidelines.

The Research 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;<sup>12</sup>
- the suitability of the study population, whether they constitute a vulnerable group, if so whether the study is 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 takes 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;<sup>13</sup>
- 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;

<sup>11</sup> For more information on accreditation and ethical review refer to Department of Health Ethics in *Health Research: Principles, Structures and Processes*, 2004. ISBN: 1-920031-04-9, [www.doh.gov.za](http://www.doh.gov.za)

<sup>12</sup> The research ethics committees should exclude trials exposing participants to substantial risks of serious harms. Thus, even if the participants exercise poor judgment, they are protected from research with unfavourable risk – benefit profiles. When reviewing research proposals, the research ethics committee must focus on ensuring that the research is ethical and present a favourable risk-benefits ratio

<sup>13</sup> Only when there is no known effective treatment is it ethical to compare a potential new treatment with a placebo.

- 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 RESEARCH REQUIRING ADDITIONAL ATTENTION

South African research ethics committees must pay special attention to protecting the welfare of certain classes of participants.<sup>14</sup> Research ethics committees may impose additional measures to protect the welfare of participants requiring additional attention. For example, research ethics committees may make it mandatory to conduct post-research investigations to review whether there was compliance with the additional measures imposed. If compliance was defective, research ethics committees may withdraw approval for the research investigation concerned.

Participants whose involvement needs additional attention include:

- Minors: Children and adolescents
- Women
- People with mental disabilities or substance abuse related disorders
- Persons in dependent relationships or comparable situations
- Prisoners
- Persons highly dependent on medical care

Types of research that need additional attention include:

- Research involving collectivities
- Research involving indigenous medical systems
- Emergency care research
- Research involving innovative therapy or interventions
- Research involving vulnerable communities
- HIV and AIDS clinical and epidemiological research

<sup>14</sup> For further, more detailed, discussion on special classes of participants, refer to CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002) Guidelines 13-17, [http://www.cioms.ch/guidelines\\_nov\\_2002\\_blurb.htm](http://www.cioms.ch/guidelines_nov_2002_blurb.htm); US Department of Health & Human Services, Office for Human Research Protections, <http://www.hhs.gov/ohrp/>.

**2.3.1 Minors:** Children and adolescents: A minor for the purposes of these guidelines is defined as a person under 21 years of age i.e. majority begins at 21 years of age.<sup>15</sup> Minors should participate in research only where their participation is indispensable to the research. Where research involving minors is proposed, a research ethics committee should determine whether the research might be equally informative if carried out with consenting adults. If so, the research ethics committee should require strong justification for the inclusion of minors. The research should investigate a problem of relevance to children. Note that all types of clinical research on minors should be scrutinized carefully.

Research involving minors should be approved only if:<sup>16</sup>

- The research interventions, including those in observational research, presents the participant with no greater than minimal risk (that is, the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine medical or psychological examinations or tests – referred to as 'negligible risk' in some guidelines); or
- The research interventions present more than minimal risk but hold out the prospect of direct benefit for the participant. The risks must be justified by the anticipated benefit; or
- The research interventions, including those in observational research, present more than minimal risk and do not hold out the prospect of direct benefit to the participant, but have a high probability of yielding generalizable knowledge. That is the risk should be justified by the risk-knowledge ratio. The risk should represent a minor increase over minimal risk. The intervention or procedure should present experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or education settings.
- In all cases, the protocol must provide sufficient information to justify clearly why minors should be included as participants.

**2.3.1.1 Consent Requirements:**<sup>17</sup> For research with minors, the following should be obtained:

- Consent from a parent or legal guardian in all but exceptional circumstances (e.g. emergencies). A caregiver (e.g. custodian, person providing long-term day-to-day care for the child) can act on behalf of a minor;
- Assent from the minor where s/he is capable of understanding;

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<sup>15</sup> Legally, a child is a person under the age of 18 (section 28(3) Constitution of the Republic of South Africa and Child Care Act no 74 of 1983). Whilst legally, a minor is a person under the age of 21 who does not have full legal capacity to act independently (s1, Age of Majority Act, no 57 of 1972). During childhood and the period of legal minority persons have special legal protection. A difficulty in South African law is that childhood ends at 18. The Children's Act, Act No. 38 of 2005 established that the age of majority drop from 21 to 18, i.e. legal majority will be attained at the end of childhood. The National Health Act 61 of 2003 refers more to 'minors' rather than 'children' in s 71 which deals with research with human subjects.

<sup>16</sup> All other legal requirements must also be met. For example, s71 of the National Health Act, Act No. 61 of 2003 requires, amongst others, that "therapeutic research" be in the best interests of the child and, and "non-therapeutic research" must be authorised by the Minister of Health. (For the purposes of these guidelines, 'therapeutic' refers to interventions that may hold out the prospect of direct benefit for the participant; whilst 'non-therapeutic' refers to interventions that may not hold out the prospect of direct benefit for the participant but results may be produced that significantly contribute to generalisable knowledge).

<sup>17</sup> Section 11 of the National Health Act, Act No. 61 of 2003 requires the health care provider primarily responsible for the users' (a person receiving treatment, section 1 of the National Health Act) treatment and the Head of the Health Establishment in question to consent to any "therapeutic research" being undertaken in that establishment.

- Any organization or person required by law, e.g. National Health Act, Act No 61 of 2003.
- A child's refusal to participate in research must be respected, i.e. such refusal settles the matter.

**2.3.1.2 Assent Requirements:** Assent means a minor's affirmative agreement to participate in research. Mere failure to object should not be construed as assent. The research ethics committee must ensure that adequate steps are outlined in the protocol to obtain the minor's assent when, in the judgement of the research ethics committee, the minor is capable of providing such assent. When the research ethics committee decides that assent is required, it must also indicate whether and how such assent must be documented.

**2.3.2 Women:** Exclusion of women as research participants has led to a lack of data needed to promote women's health. Research ethics committees should consider whether the exclusion of women is justified in terms of research priorities and the specific research question under consideration. As part of advocating improved health for women, researchers have ethical obligations to conduct research that does not perpetuate discriminations against women by unfairly or unjustifiably excluding them from study protocols.

**2.3.2.1 Women and Pregnancy:** Research ethics committees must give extra attention to research that involves women who are, or may become pregnant, because of the additional health concerns during pregnancy and the need to avoid unnecessary risk to the foetus. Reasons for excluding women from research should be adequately justified both from the point of protecting the health of a foetus and from the perspective of whether such exclusion is scientifically supportable.

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, presents 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.

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 results from rape.

**2.3.2.2 Foetuses In-Utero as Participants:** No foetus in utero may be involved as a participant 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.

**2.3.2.3 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 participant 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 participant 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.

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/or (2) determining the viability of the foetus at the termination of the pregnancy.

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.

Any activity permitted above may be conducted only if the mother is legally competent and has given informed consent after having been fully informed about the possible impact on the foetus.

**2.3.3 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 groups of people as far as research is concerned, is their capacity for reason regarding participation and comprehension of 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 mental 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 have a mental disability and/or a substance abuse related disorder/s;
- Justify the involvement, as the study population, of institutionalised people with mental disabilities;
- 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 participants; and
- Ensure that only minimal risk is involved, and that the risk is outweighed by the anticipated benefits for the participants and by the importance of the knowledge that will emanate from the research.

Persons with intellectual or mental impairment should not participate in research that might equally well be conducted with persons without those impairments.

Consent to research must be obtained from:

- the person with the intellectual or mental impairment, wherever he or she is competent to give informed consent;
- the person's legal guardian where the person is deemed not competent to do so; or
- an authority, organisation or person having that responsibility by law.

Consent cannot be given for participation in research that is contrary to the interests of the person with the intellectual or mental impairment.

The intellectually or mentally impaired person's refusal to participate in research must always be respected.

**2.3.4 Persons in Dependent Relationships or Comparable Situations:** Persons whose proposed involvement in research arises from dependent or comparable relationships need additional attention and the research ethics committee must be satisfied that their consent is both adequately informed and voluntary.

It is not possible to define such relationships exhaustively, but they include persons who are in junior or subordinate positions in hierarchically structured groups and may include relationships between:

- older persons and their caregivers;
- persons with chronic conditions or disabilities and their caregivers;
- wards of State and guardians;
- patients and health-care professionals;
- students and teachers;
- prisoners and prison authorities;
- persons with life-threatening illnesses;
- employees and employers, e.g. farm workers and their employers, members of the uniformed services and hospital staff and their employers.

**2.3.5 Prisoners:** Ethical review must take cognisance of the impact of a prisoner's incarceration on their ability to make a voluntary decision, without coercion, on whether or not to participate in research. Research studies in South Africa may involve prisoners as participants only when the ethics committee has ensured that the clinical trial involves:

- the study of the possible causes, effects, and processes of incarceration, and of criminal behaviour, provided;
- no more than minimal risk and inconvenience to the participants;
- the study of prisons as institutional structures or of prisoners as incarcerated persons,
- research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on diseases that may be more prevalent in prisons and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) only after appropriate experts have been consulted; and
- research on practices, both innovative and accepted, that have the intent and probability of improving the health or wellbeing of prisoners.

Where some prisoners may be assigned to control groups that may not benefit from the research, the research may proceed only after appropriate experts have been consulted. Research that could be conducted on a population other than prisoners should not be permitted, unless cogent motivation is presented to the research ethics committee, and the committee is satisfied that the motivation does not represent exploitative research. Research ethics committees should take into consideration the extent to which research facilitates the empowerment of prisoners as a vulnerable group.

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

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

**2.3.6 Persons Highly Dependent on Medical Care:** The involvement in research of participants who are highly dependent on medical care raises ethical issues that deserve special attention. The gravity of their medical condition may require invasive measures carrying increased risk. Researchers need to acknowledge that informed consent may be compromised by the effect of the medical condition on the participant's capacity to form an opinion or to communicate. Additionally, there may be a perception of coercion if a participant is reluctant to refuse consent for fear that it may compromise his or her medical treatment. Researchers need to consider whether an unfair burden of participation is being placed on groups such as those referred to below.

**2.3.6.1 Intensive Care Research:** Characteristic features of intensive care research are the difficulties in communicating with patients receiving ventilatory assistance and the impairment of cognition in heavily sedated individuals. Whenever possible, information regarding intensive care research should be

obtained from potential participants before their admission to that care. Because of their extreme vulnerability such persons should be excluded from all but minimally invasive observational research.

**2.3.6.2 Neonatal Intensive Care Research:** Research involving infants receiving neonatal intensive care should be conducted in strict accordance with the principles set out in the section entitled Research Involving Children. These principles do not permit research that is contrary to the child's best interests.

The small size and vulnerability of some infants are unique features of this research, which renders all but minimal intrusion likely to be contrary to the child's best interests. The collection of even small blood samples additional to those required for diagnostic purposes, or the handling of a low birth-weight infant to make observations will demand careful scrutiny.

**2.3.6.3 Terminal Care Research:** Research in terminal care is distinguished by the short remaining life expectancy of participants and potential vulnerability to unrealistic expectations of benefits.

Researchers must take care that the prospect of benefit from research participation is neither exaggerated nor used to justify a higher risk than that involved in the patient's current treatment.

Researchers must respect the needs and wishes of participants to spend time as they choose, particularly with family members

**2.3.6.4 Research Involving Persons with Impaired Capacity to Communicate:** The distinguishing features of research involving persons with impaired capacity to communicate include acute impairment states requiring medical care, as well as non-acute states. In the former, the condition and medical care may mask the person's degree of cognition and require different means of expression. In the latter, the condition may be such as to prevent the person expressing wishes at all.

**2.3.6.5 Research Involving Unconscious Persons:** The distinguishing feature of research with unconscious persons is that, because of their incapacity for cognition or communication, it is impossible for them to be informed about the research or for a researcher to determine their wishes about it. Consent to participation in research by an unconscious person must be given by others, including relevant statutory authorities, on that person's behalf. Because of their extreme vulnerability unconscious persons should be excluded from all but minimally invasive observational research.

When research procedure precludes conformity to the principle of consent, and neither the prospective participant nor the participant's representative is able to give consent in advance, a research ethics committee may approve a research project without prior consent if it is satisfied that:

- inclusion in the research project is not contrary to the interest of the patient;
- the research is intended to be therapeutic and the research intervention poses no more of a risk than that inherent in the patient's condition and alternative methods of treatment;
- the research is based on valid scientific hypotheses which support a reasonable possibility of benefit over standard care; and

- as soon as reasonably possible, the participant and the participant's relatives or legal representatives will be informed of the participant's inclusion in the research, and will be advised of their right to withdraw from the research without any reduction in quality of care.

In the case of research proposals in which it is practicable to obtain consent before including in the research a participant who is highly dependent on medical care, a research ethics committee must be satisfied that:

- adequate provision will be made for informing patients and their relatives about the research, to ensure that stress and other emotional factors do not impair their understanding of it; and
- the dependency of patients and their relatives on the medical personnel providing treatment does not affect any decision to participate.

**2.3.7 Research Involving Collectivities:** A collectivity is an expression used to distinguish some distinct groups from informal communities, commercial or social groups. Collectivities are groups distinguished by:

- common beliefs, values, social structures and other features that identify them as a separate group;
- customary collective decision-making according to tradition and beliefs;
- the custom of leaders expressing a collective view;
- members of the collectivity being aware of common activities and common interests.

Researchers must seek research ethics committee approval for research involving a collectivity when any of the following conditions apply:

- property or information private to the group as a whole is studied or used;
- the research requires the permission of people occupying positions of authority, whether formal or informal, or involves the participation of members acknowledged as representatives.

Arrangements to address these issues should follow a process of respectful negotiation, and may include:

- the manner in which anticipated or actual disagreements between the researcher and the collectivity will be resolved;
- the seeking of informed consent from both the collectivity and individual participants;
- resolution of the ownership of data and the rights of publication of research findings;
- the fair distribution of direct benefits and harms of the research among affected participants.

Research ethics committees should require that researchers provide a plan for consultation of community representatives, community involvement and feedback of results.

**2.3.8 Research Involving Indigenous Medical Systems:** Researchers must respect the cultures and traditional values of all communities. Participants involved in research of indigenous medical systems must be accorded the same degree of respect and protection from harm as participants in scientific medical research. The research must be submitted for ethics review by a registered health research ethics committee. The toxicological risk of any substance that is used on participants must be adequately assessed. Researchers should furnish proof of safety to the research ethics committee.

**2.3.9 Emergency Care Research:** The benefits of emergency care research include improved effective treatment for life-threatening conditions and improving therapies for survival and quality of life. Research into emergency medical treatment needs to involve participants who are experiencing medical emergencies.

The distinguishing feature of emergency care research however is that consent to commence a project usually has to be obtained rapidly, when the vulnerability of patients and families is likely to be greatest. Because of their extreme vulnerability, such persons should be excluded from all but minimally invasive observational research. Research ethics committee must therefore take great care when assessing emergency care research.

Moreover, the circumstances surrounding emergency care research are such that it may not always be possible to obtain consent for inclusion without delaying the initiation of treatment, and so risking a reduction of potential benefits. As such there may be circumstances in which it is not possible to obtain consent for inclusion in emergency care research. After a protocol has been presented by a researcher giving clear reasons to justify the initiation of the emergency care research without consent, a research ethics committee may approve the research without consent provided it is satisfied that:

- reasonable steps are being taken to ascertain the religious and cultural sensitivities of patients experiencing medical emergencies;
- the condition of the patient precludes the giving of consent;
- inclusion in the trial is not contrary to the interests of the patient;
- the research is intended to be therapeutic and poses no more risk than is inherent to the patient's condition or would be caused by alternative methods of treatment;
- the patient and the patient's next of kin or legal representatives will be informed as soon as is reasonably possible of the patient's inclusion in the study and of the option to withdraw from the research project at any time;
- the patient will be informed, and consent obtained, once the patient who has undergone the necessary emergency procedures has regained consciousness; and
- the research is based on valid scientific hypotheses and offers a realistic possibility of benefit over standard care.

**2.3.10 Research Involving Innovative Therapy or Intervention:** Research, which requires additional attention from research ethics committee, includes the use of any innovative therapy or intervention that is being tested on one or more patients. A research ethics committee must ensure that appropriate provision is made for the long-term care and observation of participants and for the maintenance and security of records, before commencing new therapeutic or innovative procedures

**2.3.11 Research Involving Vulnerable Communities:** South Africa is home to a number of vulnerable communities. Attributes of a vulnerable community can include one or more of the following: limited economic development; inadequate protection of human rights; discrimination on the basis of health status; limited ability of individuals in the community to provide informed consent; limited availability of health care and treatment options; and the inadequate understanding of scientific research. Where factors relating to vulnerability are an aspect of the research, the researchers should demonstrate how they will seek to redress that vulnerability. Particular caution must be exercised before undertaking research involving participants in such communities, and ethics committees must ensure that:

- persons in these communities will not ordinarily be involved in research that could be carried out in non-vulnerable communities;

- the research is relevant to the health needs and priorities of the community in which it is to be carried out;
- research participants should know that they are taking part in research and this research should be carried out only with their consent. This requires that particular attention be paid to the content, languages and procedures used to obtain informed consent;
- the research protocol does not adversely affect the routine treatment of participants, nor should it disrupt routine management protocols; and
- the research protocol demonstrates some benefit to the community involved and how feedback on the outcome of the research will be transmitted to the community.

**2.3.12 HIV/AIDS Clinical and Epidemiological Research:**<sup>18</sup> 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.

**2.3.12.1 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.

**2.3.12.1.1 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.

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.

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<sup>18</sup> 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.

**2.3.12.1.2 Placebo and HIV Preventive Vaccine Trials:** As long as there is no known effective HIV preventive vaccine, a placebo control arm should be considered ethically acceptable in an HIV preventive vaccine trial. A vaccine with proven efficacy in preventing infection or disease from HIV does not currently exist. Therefore, the use of a placebo control arm is ethically acceptable in appropriately designed protocols. Participants in the control arm of future HIV preventive vaccine trials should receive an HIV vaccine known to be safe and effective when such is available, unless there are compelling scientific reasons which justify the use of a placebo.

Compelling scientific reasons to use a placebo rather than a known effective HIV vaccine in the research population include:

- i. Evidence that the HIV vaccine is highly unlikely to be effective against the virus that is prevalent in the research population; and
- ii. Convincing reasons to believe that the biological conditions that prevailed during the initial trial demonstrating efficacy were so different from the conditions in the proposed research population, that the results of the initial trial cannot be directly applied to the research population under consideration.

All participants should receive the benefit of active promotion of HIV preventive interventions. Based on scientific requirements, the balance of risks and benefits to active versus control arms, and the wishes of participants, due consideration could be given to the use in the control arm of a vaccine to prevent a relevant condition other than HIV.<sup>19</sup>

**2.3.12.1.3 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, ongoing therapy should be according to the universal standard of care. It is the responsibility of the sponsor to provide the same standard of care for a period of ten years starting from termination of the study. Costs of this care should be borne by the sponsor.

**2.3.12.1.4 Access to Study Medications Following the Completion of a Clinical Trial:** On completion of a trial, trial participants should be referred to existing health care services, with the understanding that there is progressive implementation of state supported Anti-Retroviral Therapy (ART).

**2.3.12.2 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.

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<sup>19</sup> <http://www.sahealthinfo.org/ethics/book5control.htm>

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.

**2.3.12.2.1 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.

**2.3.12.2.2 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.

**2.3.12.2.3 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 the 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.

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

**2.3.12.3 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 participants 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.

**2.3.12.4 HIV Vaccine Research:** There are a variety of international and national vaccine initiatives in South Africa. This research is highly specialised and it raises many ethical issues. This section will not address the range of issues that are being addressed by the appropriate vaccine research groups.<sup>20</sup> 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 sub-type to the local population.

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

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<sup>20</sup> For more information on HIV vaccine research see South African Medical Research Council (2003) Guidelines on Ethics for Medical Research: HIV Preventive Vaccine Research. ISBN 1-919809-49-X (set) ISBN 1-919809-54-6

**2.3.12.5 Involvement of People Living with HIV/AIDS (PWAs):** The many tensions, dilemmas and ethical considerations 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.

**2.3.13 Other special groups:** The discussion on special groups should not be limited to those already mentioned. Other special groups/situations include: elderly or aged patients, minorities, students, persons who do not have English as a first language, employees and research necessitating ambiguous information be provided to research participants. Research ethics committees must ensure special consideration is given to all these groups, especially with regard to informed consent.

## **2.4 COMMUNICATION AND COMMUNITY INVOLVEMENT**

Research to be carried out a community level (e.g. vaccine trials) should ideally ensure adequate consultation with civil organisations that may exist within affected communities at all phases of the trial. Sponsors are encouraged to establish Community Advisory Groups (CAGs). A CAG can be viewed as a community representing body that may advocate for human rights and promote ethical conduct in clinical research; contribute to addressing and resolving grievances about the research process; give advice on accrual and retention of trial participants and voice concerns around the development, implementation and outcomes of specific clinical and related studies. Researchers are encouraged to ensure that: information flow mechanisms are developed between investigators and participating communities; and that communities are educated on the aspects of research before recruitment begins.

### **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 accredited local research ethics committee, and, if applicable, the MCC are obtained and that the trial is issued a South African Clinical Trial Register number by the Department of Health;
- 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 MCC 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 an audit by an independent auditor appointed by the sponsor, and/or an inspection by the MCC, ethics committee, or applicable regulatory authority(ies) to participants' records;
- ensure that they have the responsibility to make trial results (both positive and negative) publicly available within a reasonable timeframe (see section 4.22 for more information on trial results);<sup>21</sup>
- have the responsibility to share possible benefits of research results with participants;<sup>22</sup>

<sup>21</sup> However sponsors may retain the right to verify the scientific accuracy of the report.

<sup>22</sup> The benefits of research are to be made available to the research population and the local communities from which they were drawn, and adequate reports of the research must be made publicly accessible within a reasonable period of time. All research participants should be informed of the outcome of the research in which they were involved (<http://www.sahealthinfo.org/ethics/ethicsmonitoring.htm>)

- generate the information package for the participant, and where applicable with the sponsor;
- ensure proper safety reporting procedures.

### **3.2 PRINCIPAL INVESTIGATOR/INVESTIGATOR'S QUALIFICATIONS AND AGREEMENTS**

The Principal Investigator(PI)/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 accredited research ethics committee, and/or the MCC.

The PI/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,<sup>23</sup> in the product information and in other information sources provided by the sponsor.

The PI/investigator should be aware of, and should comply with, Good Clinical Practice (GCP) and the applicable regulatory requirements, including the registration of the clinical study with the SANCTR and reporting of Serious Adverse Events.

The PI/investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority. (See Appendix C for more information on an MCC inspection.)

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

### **3.3 ADEQUATE RESOURCES**

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

The principal 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 principal 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.

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<sup>23</sup> See ICH Guidelines:- Section 7: Investigator's Brochure for a more detailed discussion of the contents of the Investigator's Brochure.

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

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

### **3.5 INFORMED CONSENT OF TRIAL PARTICIPANTS**

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. The informed consent form must include contact details for the MCC, and the relevant research ethics committee. In all instances both written and verbal informed consent should be obtained. Where the participant is illiterate, verbal consent should be obtained in the presence of and countersigned by a literate witness.

The PI, or designated person delegated by the PI, should then seek the participant's informed consent to participate in the study in accordance with the principles outlined in the Declaration of Helsinki (Appendix A refers), 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. (See section 7 for more information on multi-centred studies.)

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 participant'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 of harm or inconveniences to the participant and, when applicable, to an embryo, fetus, or nursing infant;
- (i) The expected benefits. When there is no intended clinical benefit to the participant, the participant 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 participant, and their important potential benefits and risks;
- (k) The compensation and/or treatment available to the participant in the event of trial-related injury;
- (l) The anticipated prorated payment, if any, to the participant for participating in the trial;

- (m) The anticipated expenses, if any, to the participant for taking part in the trial;
- (n) Allow access of sponsor, MCC, National Health Research Ethics Council, relevant research ethics committee and / or other regulatory authority(ies) (pending that they have received permission to do so from the National Health Research Ethics Council) to participant records;
- (o) Provide a contact name and number of the PI and directly responsible investigator;
- (p) The identity of a sponsor and any potential conflict of interests; and
- (q) The requirement to preserve the confidentiality of the participant.
- (r) The expected duration of the subject's participation
- (s) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated
- (t) The approximate number of subjects involved in the trial.

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 offered to the participant.

### **3.6 INVESTIGATIONAL PRODUCT(S)**

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

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

Where allowed/required, the principal investigator may assign some of the principal 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 principal investigator.

The principal investigator and/or a pharmacist or other appropriate individual, who is designated by the principal investigator, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused product(s).<sup>24</sup> 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. Principal 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) and Good Manufacturing Practice (GMP) in South Africa, and the MCC regulations and conditions.

Investigational products unused at the conclusion of a trial should be disposed of in line with the MCC approved protocol.

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

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<sup>24</sup> If it is a new investigational product, the Medicines Regulatory Authority will specify the conditions under which the product is made available in South Africa.

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

### **3.7 COMPLIANCE WITH PROTOCOL**

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

The principal 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)). 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 to: (a) the ethics committee for review and approval, (b) the sponsor for agreement and, (c) the MCC. The PI must also ensure that the South African Clinical Trial Register is updated accordingly.

The principal investigator, or person designated by the principal investigator, should document and explain any changes to the approved protocol. (See Appendix B for details on clinical trial protocol and protocol amendments).

### **3.8 MONITORING AND AUDITING**

The functional 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 PI/investigator(s) should attend the initial briefing between the monitor and all staff involved in the study.

The principal investigator must be prepared to receive and be available for periodic visits by the monitor(s) and accept the implications of such visits.

In addition, the PI/investigator(s) should accept the possibility of an audit or monitoring visit by an independent auditor appointed by the sponsor, and/or an inspection by the MCC, ethics committee, or applicable regulatory authority(ies).

### **3.9 CHANGE OF PRINCIPAL AND/OR SUB-INVESTIGATOR**

If the principal and/or sub-investigator withdraw(s) 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 and/or sub-investigator (in similar form to that submitted for the original principal and/or sub-investigator) should be presented by the sponsor for approval to the relevant regulatory authority. If practicable the change in principal and/or sub-investigator should also be notified to the participants in the study, and the South African Clinical Trial Register (SANCTR) updated.

### **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 study protocol. 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 principal 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 the 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 principal 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**

Drug trials have the potential to cause short and long term ill effects. Decisions and actions relevant to the clinical management and safety of the participant in acute situations are the responsibility of the principal investigator.

The principal investigator is responsible for ensuring that adequate provisions are made for dealing with any expected and unexpected adverse events that may occur in the study participants.

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 adverse drug reactions. In such a situation appropriate therapy required to manage the adverse drug reaction 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.

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 principal 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.

The initial serious adverse event 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 research ethics committee, and the MCC.

The timeframes and format for reporting of serious adverse events, adverse events and drug reactions are described in the MCC guidelines and should be strictly adhered to.<sup>25</sup>

### **3.13 BREAKING THE TREATMENT CODE**

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

Unblinded serious adverse events should be reported to the MCC by the principal investigator via the sponsor where there is a sponsor, in writing and within a time frame and manner prescribed by the MCC in their adverse drug reaction reporting guidelines. Accidental unblinding should be reported to the MCC as a protocol violation.<sup>26</sup>

### **3.14 PROGRESS REPORTS AND FINAL STUDY REPORTS**

The principal investigator is obliged to submit progress reports as required by the sponsor, the MCC 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, adverse events and if the planned time schedule is still appropriate. The format and frequency of reporting shall be as prescribed by the relevant authorities. (E.g. Regulation 34(6) Act 101 requires that the PI must submit progress reports to the MCC every six months from the date when the clinical trial was started and provide a final report 30 days after the completion of the trial.) Also on completion of the trial, the PI, where applicable, should provide the ethics committee, MCC and other relevant regulatory authorities with a summary of the trial's outcomes and a statement that the trial has been conducted in accordance with these guidelines.

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<sup>25</sup> For more information on reporting of adverse drug reactions refer to, Medicines Control Council/Department of Health (2003) Reporting of Adverse Drug Reactions in South Africa, Version NRA2003/1, <http://www.mccza.com>

<sup>26</sup> For more information on reporting of adverse drug reactions refer to, Medicines Control Council/Department of Health (2003) Reporting of Adverse Drug Reactions in South Africa, Version MCC2003/1, <http://www.mccza.com>

### 3.15 TRIAL RESULTS

Sponsors and investigators have an ethical obligation to disseminate research results, whether positive or negative, in a timely manner. It is however important that the release of research findings be done in an ethical manner, to ensure that false expectations are not raised in a vulnerable population. Research results should not be prematurely released or published, or unreasonably delayed. It is advisable that the main results should be disseminated, using appropriate communication formats, to the participants and other interested members of the communities in which the study was conducted.<sup>27</sup>

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

The sponsor, and where there is no sponsor, the PI, is responsible for ensuring that a summary of trial results is submitted to the South African Clinical Trial Register within a year of trial completion.

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<sup>27</sup> The importance of publishing results is unquestionable, however, in recent years some investigators have released preliminary research data prematurely to the press with serious and negative consequences, particularly in relation to HIV/AIDS trials. 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.

## **4. RESPONSIBILITIES OF THE SPONSOR**

A sponsor is the person or organisation responsible for the initiation, management or financing of a clinical trial.<sup>28</sup> 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 the sponsor's roles and responsibilities 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.

### **4.1 SUBMISSION TO THE MCC FOR APPROVAL**

Before initiating a clinical trial(s) in South Africa, the sponsor and the principal investigator must obtain approval from the MCC 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.<sup>29</sup>

### **4.2 CONFIRMATION OF REVIEW BY RESEARCH ETHICS COMMITTEE**

The sponsor should obtain from the principal investigator the name and address of the relevant accredited research ethics committee and documented research ethics committee approval.

If the research 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 principal investigator/institution a copy of the modification(s) made and the date approval was given by the research ethics committee.

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

### **4.3 THE SOUTH AFRICAN CLINICAL TRIAL REGISTER (SANCTR)**

All clinical trials to be conducted in South Africa are required to be registered with the SANCTR. Registration on the SANCTR requires that a trial is approved by a Research Ethics Committee and meets the requirements of the National Regulatory Authority. SANCTR facilitates registration of trials in accordance with the World Health Organisation's International Clinical Trials Registry Platform initiative requiring prior entry of clinical trials in a public registry as a condition for publication.

Sponsors/funders are responsible for ensuring that a trial is fully registered on the SANCTR before enrolling participants. It is the responsibility of the principal investigator and the trial sponsor to communicate information required for registering the trial. For unfunded trials, the primary investigator takes responsibility for registering the trial.

Multi-site trials and multi-sponsor trials are susceptible to duplicate registration, thus care must be taken in how the trials are registered. For multi-sponsor trials it is the lead sponsor who should take responsibility for registration. It is critical that investigators and sponsors work together to ensure that a trial is registered once and only once for this national register.

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<sup>28</sup> IRB (1997)

<sup>29</sup> For more information on the NRA (MCC) go to <http://www.mccza.com>

Clinical trials are registered at <http://www.saclinicaltrials.gov.za/> via a web based data entry system called the SANCTR Toolkit.

#### **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.

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 3 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 7 on Multi-centred Studies)

#### 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 participant identification code that allows identification of all the data reported for each participant.

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 15 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 15 years or until, at least, two years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 15 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 these Guidelines, GCP, the requirements of the MCC 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 principal 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 INVESTIGATORS<sup>30</sup>**

The MCC, ethics committees and other relevant regulatory authorities require 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 participant in the trial.

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

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<sup>30</sup> Association of the British Pharmaceutical Industry Compensation 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 participant has freely consented (whether in writing or otherwise) to participate in the trial should exclude a participant from consideration for compensation under these guidelines.

For the avoidance of doubt, compensation should be paid regardless of whether the participant 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 obligation to pay compensation:

- For the failure of a medicinal product to have its intended effect or to provide any other benefit to the participant.
- For injury caused by other licensed medicinal products administered to the participant for the purpose of comparisons with the product under trial.
- To participants 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; or
  - through contributory negligence by the participant.

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 (which will depend on the level of risk the participant 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; and
- 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 participant'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 participant 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 participant but there exists a difference of opinion between sponsor and participant 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 participants) 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 participant to the sponsor, preferably via the investigator, setting out details of the nature and background of the claim and, subject to the participant 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 responsibly 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 participant to pursue a legal remedy in respect of injury alleged to have been suffered as a result of participation. Nevertheless, participants 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**

Incentives for potential trialists to submit themselves for research purposes need careful consideration. Incentives should not be so excessive so as to unfairly influence a participant's inclusion in a 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 potential participant to overlook other important considerations. The sponsor must ensure that participants are reimbursed for all reasonable costs incurred by their participation in the trial.

The sponsor must also 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.

#### **4.13 FINANCING**

The financial aspects of the trial should be documented in an agreement between the sponsor and the principal investigator/Contracted Research Organisation/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 Good Manufacturing Practice (GMP), and is coded and labeled in a manner that protects the blinding, if applicable. The labeling 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 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 Good Pharmacy Practice (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 principal 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 the MCC and other applicable regulatory authority(ies)).<sup>31</sup>

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 MCC approved protocol and/or where available, applicable regulatory requirement(s)).

The sponsor should:

- (a) Ensure timely delivery of investigational product(s) to the PI/investigator(s).
- (b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s).

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<sup>31</sup> The approval letter from the Medicines Regulatory Authority is also an authorization document to import unregistered medication under section 21 of Act 101 of 1965

- (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 MCC regulation.

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 participant 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 MCC 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. Study participants should also be informed of any new information that could adversely affect their safety.

#### **4.19 ADVERSE DRUG REACTION REPORTING**

The sponsor should expedite the reporting of all adverse drug reactions (ADRs) that are both serious and unexpected to all concerned, including investigator(s)/institutions(s), research ethics committee(s), and to the MRA.<sup>32</sup>

The expedited reporting should occur within the timeframe and format specified by the MCC. Serious unexpected adverse events suspected to be related to the investigational product/s or investigation procedures should be reported to the relevant research ethics committee as soon as possible, and in line with the requirements of the MCC adverse events reporting guideline.

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 a six monthly basis to all appropriate parties including, investigator(s), research ethics committee(s), and to the MCC.

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<sup>32</sup> For more information on reporting of adverse drug reactions refer to, Medicines Control Council/Department of Health (2003) Reporting of Adverse Drug Reactions in South Africa, Version MCC2003/1, <http://www.mccza.com>

The sponsor should submit to the MCC and research ethics committees all safety updates and periodic reports, as required by applicable regulatory requirement(s). Review of reported serious and unexpected adverse drug 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 are clearly documented within the study protocol. Such events must be reported to all concerned including the PI/investigator(s)/institutions(s), the research ethics committee(s), and the MCC.

#### **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 research ethics committee and the MCC.

The results of all trials must be communicated to the appropriate ethics committee, the MCC 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 MCC 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 relevant accredited research ethics committee, the MCC and the Department of Health via the South African National Clinical Trial Register. Results should be disclosed within one year of study completion (i.e. one year after the actual date that analysis is concluded for the protocol). Results of trials of commercially developed drugs may be disclosed within one year of first product launch. For collaborative studies and multi-centre trials, publication conditions need to be clearly outlined in the protocol, and approved by the relevant regulatory authorities.

#### **4.23 NON-COMPLIANCE PROCEDURES**

The sponsor has an ethical duty to inform the appropriate research ethics committee and MCC 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.

## 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."<sup>33</sup> 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, and that the rights and well-being of the participants are protected.

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 principal investigator.

The monitor or other contact person, appointed by the sponsor and known to the principal 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, these Guidelines, the Declaration of Helsinki, Standard Operating Procedures (SOPs), relevant legislation and good clinical research practice;

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<sup>33</sup> MRC (1998) Guidelines for Good Clinical Practice in Clinical Trials, 20 Park Crescent, London, W1N 4AL, United Kingdom

- 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 research ethics committee and check that it is accredited by the National Health Research Ethics Council;
- confirm that the regulatory requirements, research 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 6);
- 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 MCC; and
- obtain a copy of the SANCTR number issued by the 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 principal 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 dependent 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 every six months to fulfil the reporting requirements of the sponsor, ethics committees and MCC.

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 principal investigator.

**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 multinational 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 MCC.

The person responsible for auditing must submit a report to the MCC 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:** Non-compliance 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 identify serious and/or persistent non-compliance on the part of an investigator, the sponsor should terminate the investigator's participation in the trial. The sponsor must promptly notify the MCC, ethics committee and/or other relevant regulatory authority(s) of serious and/or persistent non-compliance on the part of an investigator, and also promptly inform the relevant authorities when an investigator's participation is terminated because of non-compliance.

**5.2.5 Premature Termination or Suspension of a Trial:** If a trial is prematurely terminated or suspended, the sponsor should promptly inform the principal investigators, and the MCC of the termination or suspension and the reason(s) for the termination or suspension. The research 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). The sponsor is also responsible for ensuring that the SANCTR is updated accordingly.

**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).<sup>34</sup>

### 5.3 INSPECTIONS (Appendix C)

As prescribed by regulations of the MCC (Medicines and Related Substances Act, 1965), the MCC 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 MCC by the investigator or the sponsor. Inspections may include a data audit. The MCC 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.

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<sup>34</sup> In South Africa regulations require this to be done in 30 days.

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

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

## **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 results must be recorded in the SANCTR of the Department of Health within one year of completion of the study. (See sections 4.3 and 4.22 for further details on SANCTR.)

#### **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 privacy legislation and the South African Constitution. 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 MCC, 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 15 years or until, at least, two years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 15 years have elapsed since the formal discontinuation of clinical development of the investigational product, which is longer than the time to destruction interval in some hospitals and institutions. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s).

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 MCC, 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 principal investigator; i.e. 15 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; and
- 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 MCC, an accredited ethics committee and other relevant regulatory authorities.

The person responsible for the overall clinical care of the patient should be closely involved 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. The principal investigator or overall project manager should therefore 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.

For multi-centre trials the sponsor should ensure that:<sup>35</sup>

- All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the MCC, and given approval/favourable opinion by the research ethics committee;
- The CRFs are designed to capture the required data at all multi-centre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data;
- 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; and
- Communication between investigators is facilitated.

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<sup>35</sup> 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. RESEARCH ETHICS COMMITTEES<sup>36</sup>**

### **8.1 RESPONSIBILITIES**

To be ethical, all health research on animals and on human participants must be scientifically sound. Ethics are as important as scientific considerations when reviewing a research project. An independent South African based research ethics committee must review the ethical and scientific rigour of all clinical trials to be conducted in South Africa.

The primary role of a research ethics committee is to safeguard the dignity, rights, safety, and well-being of all trial participants. The primary responsibility of each member is to decide, independently, whether in his or her opinion, the conduct of the proposed clinical trial will so protect participants.

Institutions or organisations that undertake research involving human participants should ensure that there are adequate resources to establish and maintain a research ethics committee.<sup>37</sup>

Terms of reference must be set out by the institution or organisation when establishing a research ethics committee. Terms of reference must include the scope of its responsibilities, remuneration, if any, for members.

The institution or organisation must accept legal responsibility for the decision and advice received from the research ethics committee and indemnify the research ethics committee's members.

Researchers without affiliation to an institution or organisation with a research ethics committee must ensure that their projects are approved by an accredited research ethics committee.

### **8.2 ETHICS AND LEGISLATION**

The National Health Act, 2003 (Act No.61 of 2003) proposes the functions of research ethics committees include:

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

The National Health Research Ethics Council is established in terms of the National Health Act, 2003 (Act No.61 of 2003). The role of the Council is to promote and monitor compliance of South African research ethics committees with relevant legislation and regulations, ethical guidelines and standards. All research ethics committees must be registered with and accredited by the National Health Research Ethics Council.

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<sup>36</sup> This section should be read in conjunction with the Department of Health ethics guidelines i.e. Department of Health (2004) Ethics in Health Research: Principles, Structures and Processes. ISBN: 1-920031-04, <http://www.doh.gov.za>

<sup>37</sup> Declaration made by representatives of South African ethics committees in a meeting held in Johannesburg on 31<sup>st</sup> October 2005, supports this statement. The Declaration states: "In the interests of protecting human research participants, we, as representatives of research ethics committees for health research declare that the respective committees should be:

- Autonomous and free of any conflicts of interest that impact on our ethical decision-making processes based on the Department of Health guidelines "Ethics in Health Research: Principles, Structures and Processes", and the Constitution of South Africa; and
- Adequately supported by our institutions in order to ensure optimal human research participant protections."

### 8.3 COMPOSITION

The research 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 research ethics committee must be:

- Representative of the communities they serve and reflect the demographic profile of the population of South Africa;
- Have at least nine members, with 60% representing a quorum;
- Have a chairperson;
- Include members of both gender and not more than 70% of its members should either be male or female;
- Include at least two lay person who have no affiliation to the institution, are not currently involved in medical, scientific or legal work and preferably are from the community in which the research is to take place;
- Include at least one member with knowledge of, and current experience in areas of research that are likely to be regularly considered by the research ethics committee;
- Include 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);
- Include at least one member who as professional training in both qualitative and quantitative research methodologies;
- Include at least one member who is legally trained;
- The institution or organisation must ensure that the membership is equipped to address all relevant considerations arising from the categories of research likely to be submitted to it; and
- adequately informed on all aspects of a research protocol, including its scientific and statistical validity, that are relevant to deciding whether the protocol is acceptable on ethical grounds.

### 8.4 APPOINTMENT OF MEMBERS

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

### 8.5 PROCEDURES

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

- Frequency of meetings;
- Preparation of agenda and minutes;
- Distribution of papers prior to meetings;
- Presentation of research protocols;
- Presentation of all documents and other materials used to inform potential research participants;
- Quorum and methods of decision-making;
- Requirements for submission of research projects for ethical approval;
- Registration of applications;
- Timely review and notification of decisions to researchers;
- The recording in writing of decisions made by the committee and reasons for the decisions;

- Confidentiality of the content of the protocols and of a committee's proceedings;
- Reporting of adverse events;
- Reporting of amendments to protocols;
- Access to documents;
- Regular monitoring;
- Complaints procedures;
- Procedures for easy and adequate access to member of research ethics committees;
- Fees charged, if any; and
- End of trial review.

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

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

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

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

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

Protocols for clinical trials to be conducted in community settings must include a clear plan on how the communities will be consulted or involved in the research process, and how they will be kept informed.

Communication between sponsors and ethics committees should be directed through the principal investigator. (In some situations, particularly in the private sector, the principal investigator may be an employee of the sponsoring company or of a clinical research organisation.)

All documents and other material used to inform potential participants should be approved by the research ethics committee, including plain-language information sheets, consent forms, questionnaires, advertisements and letters.

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

## 8.6 ADVOCACY ROLE AND INTERPRETERS

**8.6.1 Advocacy:** A research ethics committee must consider whether persons playing an advocacy role for any participant or group of participants should be invited to the research ethics committee meeting to ensure informed decision-making and understanding by these participants.

**8.6.2 Interpreters:** Where a trial involves the participation of person unfamiliar with the language in which the trial is to be conducted, a research ethics committee must ensure that:

- The participant information statement has been translated into the participants' language of choice;
- Every effort has been made on the behalf of the principal investigator to ensure that participants understand the participant information sheet; and
- An interpreter is present during discussions with the participants about the project.

As a rule, the interpreter should be independent, but when the research protocol is of minimum risk, a relevant language speaking relative or friend of the participant may be acceptable.

## 8.7 EXPEDITED REVIEWS FOR MAXIMAL PUBLIC BENEFIT

A research ethics committee may establish procedures for expedited review of clinical trials when this is in the public interest. For example, expedited review and approval may be considered for a trial where participants have a disease that may be rapidly fatal.

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

## 8.8 RECORDS

The research 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 15 years after completion of the trial and make them available upon request from the regulatory authority(ies).

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

## 8.9 MONITORING

A research ethics committee has the responsibility to ensure that the conduct of all clinical trials approved by the research ethics committee is monitored. The frequency and type of monitoring should reflect the degree of risk to participants in the trial.

A research ethics committee must request at regular intervals, at least annually, reports from the principal investigator, on matters including:

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

Research ethics committees should inform the principal investigator, in writing, of any decisions made after the review of progress reports has been completed.

A research ethics committee may recommend and adopt any additional appropriate mechanism for monitoring, including the random inspection of trial sites, data and signed consent forms, and records of interviews, with prior consent of research participants.

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

- Serious or unexpected adverse events on participants;
- Proposed changes in the protocol; and
- Unforeseen events that might affect continued ethical acceptability of the project.

A research ethics committee, as a condition of approval of the research protocol, may require the principal investigator to inform the committee, giving reasons, if the clinical trial is discontinued before expected date of completion. (Section 4.20 refers).

## **8.10 COMPLAINTS**

Each research ethics committee should establish complaints procedures. Any person has the right to forward a complaint to the National Health Research Ethics Council if the response of the research ethics committee is considered inadequate.

## **8.11 SUSPENSION OR DISCONTINUATION OF RESEARCH**

Where a research ethics committee is satisfied that such circumstances have arisen that a clinical trial is not being conducted in accordance with the approved protocol and that, as a result, the welfare and rights of participants are not or will not be protected, the research ethics committee may withdraw approval. The research ethics committee shall also inform the principal investigator and the institution or organisation of its actions, and shall recommend that the trial be discontinued or suspended or that other appropriate steps be taken.

Where ethical approval has been withdrawn, a principal investigator must discontinue the trial and comply with any special conditions required by the research ethics committee.

## **8.12 DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST<sup>38</sup> (Appendix E)**

Institutions including organisations sponsored to conduct clinical trials and research 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 decisions regarding other people.

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<sup>38</sup> Joint NH& MRC.AVCC Statement and Guidelines on Research Practice. Australia, 1990; Canadian Code of Ethical Conduct for Research Involving Humans, May 1997

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 research ethics committees or other regulatory authorities any conflict of interest which has a potential to influence the trial and its conduct.

Members of research 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 research 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.

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## **APPENDIX A:**

### **ICH Guideline for Good Clinical Practice and World Medical Association Declaration of Helsinki**

#### ICH Guideline for Good Clinical Practice (GCP)

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

## **WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI<sup>39</sup>**

### **Ethical Principles for Medical Research Involving Human Subjects**

Adopted by the 18<sup>th</sup> WMA General Assembly, Helsinki, Finland, June 1964, and amended by the

29<sup>th</sup> WMA General Assembly, Tokyo, Japan, October 1975

35<sup>th</sup> WMA General Assembly, Venice, Italy, October 1983

41<sup>st</sup> WMA General Assembly, Hong Kong, September 1989

48<sup>th</sup> WMA General Assembly, Somerset West, Republic of South Africa, October 1996

and the 52<sup>nd</sup> WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

### **INTRODUCTION**

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles 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.

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 fulfilment of this duty.

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."

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

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.

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.

In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are 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.

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 requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

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<sup>39</sup> The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

## **BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH**

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally 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.

Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

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.

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.

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

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks 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.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

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.

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 results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the 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.

In any research on 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.

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.

For a research subject who is legally incompetent, physically or mentally 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.

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.

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 characteristic of the research population. The specific reasons 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 the individual or a legally authorized surrogate

Both authors and publishers have ethical obligations. 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 principles laid down in this Declaration should not be accepted for publication.

#### **ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE**

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 protect the patients who are research subjects.

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.<sup>40</sup>

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<sup>40</sup> Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

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.

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.

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 made 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.

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The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

**Note: Note of Clarification on paragraph 30 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

## APPENDIX B

### CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)<sup>1</sup>

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.<sup>2</sup>

#### 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(es).
- 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.

## APPENDIX C:

# DETAILS OF AN INSPECTION BY THE NATIONAL REGULATORY AUTHORITY

### **1. WHAT DOES AN INSPECTION INVOLVE?**

The inspection may involve:

- a comparison of the practices and procedures of the clinical investigator with the commitments made in the application to conduct a clinical trial;
- a comparison of the data submitted to the sponsor and regulatory authority with the source data; and/or
- a system inspection of the sponsor, clinical laboratory or CRO generating data for submission to regulatory authorities. This may include inspection of both the clinical facility and analytical facility.

### **2. THE INSPECTION**

Details of the various phases of an inspection, including pre-inspection contact; the opening meeting and the actual inspection are outlined below:

- 2.1 Pre-Inspection Contact:** Where appropriate, appointments for inspection of an investigational site should be made telephonically. A written confirmation of the inspection date, time and program (if applicable) may be forwarded to the site, the sponsor company or the CRO. The Medical Director of the relevant pharmaceutical company must also 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 time span between initial contact and actual inspection should be as short as possible. Undue delay of the inspection on the part of the clinical investigator needs to be investigated.
- 2.2 Opening Meeting:** The purpose of this meeting is for the Inspector(s) to explain the purpose of the inspection, i.e. routine or for -cause, to outline the scope of the inspection and to obtain a brief review of the organisation of the site being inspected.
- 2.3 The Inspection Purpose:** The overall purpose of the conduct of the inspection should be to establish whether the investigator has fulfilled his/her GCP responsibilities. This includes the following:
- To ascertain 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 investigator has sufficient time to conduct and complete the clinical study,
  - To ensure that the investigator 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 participants or facilities away from the study in hand.
  - 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 and National Regulatory Authority approval has been obtained.
  - To determine in what manner the investigational products are handled and stored, and that investigational products are dispensed to study participants 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 participants is respected (by all persons involved). to ensure that the investigator observes the following points particularly related to medical care:

In addition, the investigator needs to provide retrospective data on numbers of participants 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 also needs to provide an up-to-date curriculum vita.

The Investigator is medically responsible for those participants who are under his/her care for the duration of the study and must ensure that appropriate medical care is maintained after the study. Where appropriate, fully functional resuscitation equipment should be immediately available in case of emergency.

Clinical significant abnormal laboratory values or clinical observations must be followed up after completion of the study.

### **3. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL**

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority (ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated:

- 1) before the clinical phase of the trial commences,
- 2) during the clinical conduct of the trial, and
- 3) after completion or termination of the trial.

A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable. Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files. Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

### 3.1 Before the Clinical Phase of the Trial Commences:

During this planning stage the following documents should be generated and should be on file before the trial formally starts

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
3.1.1 INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
3.1.2 SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	
3.1.3 INFORMATION GIVEN TO TRIAL PARTICIPANT – INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent	X	X
– ANY OTHER WRITTEN INFORMATION	To document that participants will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
– ADVERTISEMENT FOR PARTICIPANT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
3.1.4 FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
3.1.5 INSURANCE STATEMENT (where required)	To document that compensation to participant(s) for trial-related injury will be available	X	X
3.1.6 SIGNED AGREEMENT BETWEEN INVOLVED PARTIES e.g.	To document agreements		
– investigator/institution and sponsor		X	X
– investigator/institution and CRO		X	X (WHERE REQUIRED)
– sponsor and CRO			X
– investigator/institution and authority(ies) (where required)		X	X
3.1.7 DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB)/ INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: – protocol and any amendments – CRF (if applicable) – informed consent form(s) – any other written information to be provided to the participant(s) – advertisement for participant recruitment (if used) – participant compensation (if any) – any other documents given approval/favourable opinion	To document that the trial has been participant to IRB/IEC review and given approval/ favourable opinion. To identify the version number and date of the document(s)	X	X
3.1.8 INSTITUTIONAL REVIEW BOARD/ INDEPENDENT ETHICS COMMITTEE COMPOSITION	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
<b>3.1.9 REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL (where required)</b>	To document appropriate authorisation/ approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
<b>3.1.10 CURRICULUM VITAE AND/ OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)</b>	To document qualifications and eligibility to conduct trial and/or provide medical supervision of participants	X	X
<b>3.1.11 NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL</b>	To document normal values and/or ranges of the tests	X	X
<b>3.1.12 MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/ TESTS – certification or – accreditation or – established quality control and/or external quality assessment or – other validation (where required)</b>	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
<b>3.1.13 SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)</b>	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the participants		X
<b>3.1.14 INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or Investigator's Brochure)</b>	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial related materials	X	X
<b>3.1.15 SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS</b>	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
<b>3.1.16 CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED</b>	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
<b>3.1.17 DECODING PROCEDURES FOR BLINDED TRIALS</b>	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining participants' treatment	X	X (third party if applicable)
<b>3.1.18 MASTER RANDOMISATION LIST</b>	To document method for randomisation of trial population		X (third party if applicable)
<b>3.1.19 PRE-TRIAL MONITORING REPORT</b>	To document that the site is suitable for the trial (may be combined with the trial initiation monitoring report)		X
<b>3.1.20 TRIAL INITIATION MONITORING REPORT</b>	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with the pre-trial monitoring report)	X	X

### 3.2 During the Clinical Conduct of the Trial:

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
<b>3.2.1 INVESTIGATOR'S BROCHURE UPDATES</b>	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
<b>3.2.2 ANY REVISION TO:</b> – protocol/amendment(s) and CRF – informed consent form – any other written information provided to participants – advertisement for participant recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X
<b>3.2.3 DATED, DOCUMENTED APPROVAL/ FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:</b> – protocol amendment(s) – revision(s) of: – informed consent form – any other written information to be provided to the participant – advertisement for participant recruitment (if used) – any other documents given approval/ favourable opinion – continuing review of trial (where required)	To document that the amendment(s) and/or revision(s) have been participant to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X
<b>3.2.3 REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/ NOTIFICATIONS WHERE REQUIRED FOR:</b> – protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
<b>3.2.4 CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUBINVESTIGATOR(S)</b>	See 3.1.10	X	X
<b>3.2.5 UPDATES TO NORMAL VALUE(S)/ RANGE(S) FOR MEDICAL/LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL</b>	To document normal values and ranges that are revised during the trial (see 3.1.11)	X	
<b>3.2.6 UPDATES OF MEDICAL/LABORATORY/TECHNICAL PROCEDURES/TESTS</b> – certification or – accreditation or – established quality control and/or external quality assessment or – other validation (where required)	To document that tests remain adequate throughout the trial period (see 3.1.12)	X (where required)	X
<b>3.2.7 DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT</b>	See 3.1.15	X	X
<b>3.2.8 CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS</b>	See 3.1.16		X

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
<b>3.2.9 MONITORING VISIT REPORTS</b>	To document site visits by, and findings of, the monitor		X
<b>3.2.10 RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS</b> – letters – meeting notes – notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
<b>3.2.11 SIGNED INFORMED CONSENT FORMS</b>	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each participant in trial. Also to document direct access permission (see 3.1.3)	X	
<b>3.2.12 SOURCE DOCUMENTS</b>	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
<b>3.2.13 SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)</b>	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
<b>3.2.14 DOCUMENTATION OF CRF CORRECTIONS</b>	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
<b>3.2.15 NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS</b>	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa.	X	X
<b>3.2.16 NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION</b>	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa	X (where required)	X
<b>3.2.17 NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION</b>	Notification by sponsor to investigators of safety information in accordance with the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa	X	X
<b>3.2.18 INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)</b>	Interim or annual reports provided to IRB/IEC and to authority(ies) in accordance with the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa	X	X (where required)
<b>3.2.19 PARTICIPANT SCREENING LOG</b>	To document identification of participants who entered pre-trial screening	X	X (where required)

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
<b>3.2.20 PARTICIPANT IDENTIFICATION CODE LIST</b>	To document that investigator/institution keeps a confidential list of names of all participants allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any participant	X	
<b>3.2.21 PARTICIPANT ENROLMENT LOG</b>	To document chronological enrolment of participants by trial number	X	
<b>3.2.22 INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE</b>	To document that investigational product(s) have been used according to the protocol	X	X
<b>3.2.23 SIGNATURE SHEET</b>	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
<b>3.2.24 RECORD OF RETAINED BODY FLUIDS/TISSUE SAMPLES (IF ANY)</b>	To document location and identification of retained samples if assays need to be repeated	X	X

### 3.3 After Completion or Termination of the Trial:

After completion or termination of the trial, all of the documents identified in sections 3.1 and 3.2 should be in the file together with the following:

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
<b>INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE</b>	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to participants, returned by the participants, and returned to sponsor	X	X
<b>DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION</b>	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at Site)	X
<b>COMPLETED PARTICIPANT IDENTIFICATION CODE LIST</b>	To permit identification of all participants enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
<b>AUDIT CERTIFICATE (if available)</b>	To document that audit was performed		X
<b>FINAL TRIAL CLOSE-OUT MONITORING REPORT</b>	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
<b>TREATMENT ALLOCATION AND DECODING DOCUMENTATION</b>	Returned to sponsor to document any decoding that may have occurred		X
<b>FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)</b>	To document completion of the trial	X	
<b>CLINICAL STUDY REPORT</b>	To document results and interpretation of trial	X (if applicable)	X

#### **4. 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 inspector should extend the inspection as the facts evolve. The inspection conducted should be sufficient in scope to determine compliance with Good Clinical Practice. The inspector should not attempt to evaluate scientific data during the inspection, but only verify documentation and validate data.

An inspection must include the following checks:

- The protocol, included amendments must be signed by the investigator.
- Ethics Committee and regulatory approval documentation must be verified.
- Signed informed consent documents must be validated. The signatures need to be checked against evidence on patient files. It must be determined whether written informed consent was obtained for all participants prior to the entry into the study and whether this was recorded in the participants medical records. A copy of the information presented orally must be obtained.
- Participant 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 inspected participants did exist and were 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 record forms.

The following also need to be determined:

- whether the number and type of participants entered into the study were confined to the protocol limitations
- whether the inclusion and exclusion criteria as specified in the protocol were followed
- observations, information, and data condition of the participants at the time of entering into the trial.
- observations and data on the condition of the participant 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 participant 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 sponsor.

#### **5. TRIAL MEDICATION**

The following are important in an inspection with regard to 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.

## **6. 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?

## **7. POST-INSPECTION MEETING**

At the post inspection meeting the inspectors 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 should be in line with the report written by the inspectors.

Important matters include:

- When significant violations of GCP are observed, 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 guide to what should be included in an abbreviated report:

- The comparison of raw data recorded in 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.)
- There should be a statement about the trial medication accountability records
- There should be a statement about protocol adherence, which should be characterised and quantified.
- There should be a statement about the obtaining of informed consent from each participant.
- There should be a statement identifying the specific individual responsible for each significant aspect of the study.
- There should be a statement on follow-up of adverse experiences (including death) if any occurred.
- 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.
- All clinical investigator inspections 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 verification on specific areas of the study or may expand the data verification 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:**

### **MCC CLINICAL TRIAL EVALUATION CHECK-LIST (Draft)**

#### **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 sufficiently described?
- Are 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 investigators 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 withdraw 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 a local accredited research ethics committee?

## **APPENDIX E:**

### **DISCLOSURE OF CONFLICTING INTERESTS<sup>42</sup>**

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
  - (a) 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.
0. 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:
  - ( ) 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
  - ( ) 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.

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<sup>42</sup> 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: 8 December 1998

## APPENDIX F: GLOSSARY

The definitions given below apply specifically to the terms used in this guideline. They may have a different meaning in other contexts.

### **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).

### **Adverse Event (AE)**

Any untoward medical occurrence in a clinical trial participant or clinical investigation participant 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).

### **Amendment (to the protocol)**

See Protocol Amendment.

### **Applicable Regulatory Requirement(s)**

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

### **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.

### **Audit of a trial**

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, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

### **Audit Certificate**

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

## **Audit Report**

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

## **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 participant(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

## **Care-giver**

Any person other than a parent or guardian, who factually cares for a child and includes-

- (a) a foster parent;
- (b) a person who cares for a child with implied or express consent of a parent or guardian of the child;
- (c) a person who cares for a child whilst the child is in temporary safe care;
- (d) the person at the head of a child and youth care centre where a child has been placed;
- (e) the person at the head of a shelter; and
- (f) a child and youth care worker who cares for a child who is without appropriate family care in the community.

## **Case Report Form (CRF)**

A printed, optical, or electronic document designed to record data on each trial participant during the course of the trial as defined by the protocol. The data should be collected by procedures, which guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.

## **Clinical Trial/Study**

Any investigation in human participants (including patients and other volunteers) 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 their safety and/or efficacy.

Clinical trials are generally classified into Phases I to IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology do exist. A brief description of the individual phases, based on their purposes as related to clinical development of pharmaceutical products, are given below:

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### **Phase I**

These are the first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety, and a first outline of the pharmacokinetic and, where possible, a pharmacodynamic profile of the active ingredient in humans.

### **Phase II**

These trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess short-term safety of the active ingredient in patients suffering from a disease or condition for which the

active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

### **Phase III**

Trials in larger (and possibly varied) patient groups with the purpose of determining the short and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically-relevant drug interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

### **Phase IV**

Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same scientific and ethical standards as applied in premarketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

### **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).

### **Comparator (Product)**

A pharmaceutical or other product (which may be a placebo) used as a reference in a clinical trial.

### **Compliance (in relation to trials)**

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

### **Confidentiality**

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

### **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.

### **Coordinating Committee**

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

### **Coordinating Investigator**

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

### **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.

### **Direct Access**

Permission to examine, analyse, 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.

### **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.

### **Essential Documents**

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

### **Good Clinical Practice (GCP)**

A standard for clinical trials/studies which encompasses the design, conduct, performance, monitoring, termination, auditing, recording, analyses, and reporting and documentation of clinical trials/studies and which ensures that the trials/studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented and the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

### **Good Manufacturing Practice (GMP)**

That part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

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.

**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.

**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.

**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) 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). (see Appendix B).

**Institution (medical)**

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

**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.

**Interim Clinical Trial/Study Report**

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

**Investigational Product (Synonym: Study 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.

**Investigational labelling**

Labelling developed specifically for products involved in a clinical trial

**Investigator (Principal 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 Sub investigator.

### **Investigator/Institution**

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

### **Investigator's Brochure**

A collection of data for the investigator consisting of all the relevant information on the investigational product(s) including chemical and pharmaceutical data and toxicological, pharmacokinetic and pharmacodynamic data obtained from studies in animals as well as in humans, and the results of earlier clinical trials. There should be adequate data to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new data are generated, the investigator's brochure must be updated (see Investigator's Brochure).

### **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.

### **Medicines Control Council**

The Medicines Control Council (MCC) is a local institution that regulates the performance of clinical trials and registration of medicines and medical devices for use in specific diseases. The Medicines Regulatory Authority/MRA (secretariat to the MCC) coordinates applications and forward them to a relevant MCC sub-committee that is responsible to ensure that all clinical trials of both non-registered medicines and new indications of registered medicines comply with the necessary requirements for safety, quality and efficacy.

Applications for clinical trials and for registration of medicines and medical devices are reviewed by a MCC expert committee, which considers amongst other issues the scientific, medical and ethical issues of the applications. Reports on the progress of the study are sent to the MCC on a regular basis. Proof of safety, quality and efficacy must be submitted when applying to the MCC for approval and registration of a medicine for use in South Africa. For more information on the MCC refer to <http://www.mccza.com>

### **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).

### **Monitor**

A person appointed by, and responsible to the sponsor or Contract Research Organisation (CRO) for the monitoring and reporting of the trial and for verification of data.

### **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.

### **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.

### **Medicines Regulatory Authority (MRA)**

See Medicines Control Council (MCC).

### **National Health Research Ethics Council (NHREC)**

This body will have overall responsibility to promote, ensure and monitor compliance by research ethics committees in South Africa with relevant legislation, regulations and guidelines. In so doing, the National Health Research Ethics Council will accredit and audit the performance of research ethics committees. It has been established under the National Health Act, Act No. 61 of 2003. This body reports directly to the Minister of Health and is provided with secretariat support from the research directorate of the Department of Health.

### **Nonclinical Study**

Biomedical studies not performed on human subjects.

### **Opinion (in relation to Research Ethics Committee)**

The judgement and/or the advice provided by a Research Ethics Committee (REC).

### **Original Medical Record**

See Source Documents.

### **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.

### **Protocol Amendment**

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

### **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).

### **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.

### **Randomisation**

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.

### **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. These bodies are sometimes referred to as competent authorities.

## **Research Ethics Committee (REC)**

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 Research Ethics Committees may differ among countries, but should allow the Research Ethics Committee to act in agreement with GCP as described in this Guideline. Research Ethics Committees must be registered and accredited by the National Health Research Ethics Council (NHREC).

## **Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)**

An event that is associated with death, admission to hospital, prolongation of a hospital stay, persistent or significant disability or incapacity, or is otherwise life-threatening in connection with the clinical trial.

## **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).

## **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).

## **South African National Clinical Trials Register (SANCTR)**

The South African National Clinical Trials Register is a central publicly accessible clinical trials register. It provides the South African public with updated information on clinical trials on human subjects being conducted in South Africa. More specifically SANCTR provides information on a trial's purpose; who can participate, where the trial is located, and contact details. For more information on SANCTR go to: [www.saclinicaltrials.gov.za](http://www.saclinicaltrials.gov.za)

## **Sponsor**

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

## **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.

## **Standard Operating Procedures (SOPs)**

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

### **Sub investigator**

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.

### **Patient/Trial Participant**

An individual who participates in a clinical trial, either as a recipient of the investigational/pharmaceutical product(s) or as a control. The individual may be:

- a healthy person who volunteers to participate in a trial;
- a person with a condition unrelated to the use of the investigational/pharmaceutical product;
- a person (usually a patient) whose condition is relevant to the use of the investigational/pharmaceutical product.

### **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.

### **Trial Site**

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

### **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).

### **Vulnerable participants**

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.

Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable participants include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

### **Well-being (of the trial participants)**

The physical and mental integrity of the participant(s) participating in a clinical trial.

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