

South African Good Clinical Practice: Clinical Trial Guidelines



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PREAMBLE

The South African Good Clinical Practice: Clinical Trial Guidelines promote good practice in the conduct of clinical trials in South Africa. Compliance with these guidelines is mandated by Section 90(s) and 72(6)(c) of the National Health Act, Act No. 61 of 2003 as well as Regulation 30 of the Medicines and Related Substances Act, Act No. 101 of 1965, as well as the national research ethics guidelines: *Ethics in Health Research: Principles, Processes and Structures* Department of Health 2015 (or its successor).

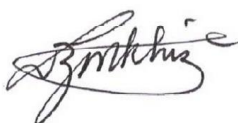
This is the third edition of the South African Guidelines for Good Practice in the Conduct of Clinical Trials involving human participants (referred to as SA GCP 2020), which supersedes the Guidelines published in 2006. The revision of the Guidelines was done in collaboration by representatives from the Department of Health, the South African Health Product Regulatory Authority (SAHPRA) and the National Health Research Ethics Council (NHREC).

The Guidelines address investigators, research ethics committees, pharmaceutical manufacturers and other sponsors of research, medicines regulatory authorities, trial participants, the general public and all persons with an interest in clinical trials research in South Africa.

The Guidelines have been carefully revised to align with the Department of Health Ethics in Health Research Guidelines 2nd edition 2015 (DoH 2015). It is important for users to familiarise themselves with the clear alignment between DoH 2015 and SA GCP 2020 so that they design, plan, manage and conduct their clinical trials in accordance with the ethical principles and values that underpin their practical application to clinical trials.

The updated Guidelines encourage improved more efficient approaches to clinical trial design, conduct, oversight, recording and reporting, to ensure continued adherence to the highest ethical and scientific standards to promote protection of participants as well as validity of trial results.

The Guidelines apply to both academic and contract clinical research, and are intended to apply to all stages of health product development - both before and after product registration and marketing. The Guidelines apply, in whole or in part, to biomedical research in general. Further, they provide a resource for journal editors to assist with determining acceptability of reported research for publication and, specifically, of any study that could influence the use of or the terms of registration of the pharmaceutical product concerned. In addition, the Guidelines are an educational tool for everyone who engages in biomedical research, especially every newly trained clinician.



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The editorial team relied on their experience and knowledge, on experts' advice sought through consultation with industry, academic research ethics committees and various other interested parties, available literature, various country experiences, and internationally accepted standards and guidelines.

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ACRONYMS

ABPI:	Association of the British Pharmaceutical Industry
ADR:	Adverse Drug Reaction
AEs:	Adverse Events
ALCOA-CCEA:	Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available)
CGT:	Cell and Gene Therapy
CIOMS:	Council for International Organizations of Medical Sciences
COI:	Conflict of Interest
Co-PI:	Co-Principal Investigator
CRF:	Case Report Form
CRO:	Contract Research Organization
CTA:	Clinical Trial Agreement
CV:	Curriculum Vitae
DSMB:	Data Safety Monitoring Board
DoH:	Department of Health
GCP:	Good Clinical Practice
GCLP:	Good Clinical Laboratory Practice
GMP:	Good Manufacturing Practice
GPP:	Good Pharmacy Practice
HPCSA:	Health Professions Council of South Africa
IB:	Investigator's Brochure
ICH:	International Council of Harmonisation
IP:	Investigational Product
NCE:	New Chemical Entity
NHA:	National Health Act
NHRC:	National Health Research Committee
NHREC:	National Health Research Ethics Council
NPI:	National Principal Investigator
PI:	Principal Investigator
PHRC:	Provincial Health Research Committees
REC:	Research Ethics Committee
SAE:	Serious Adverse Event
SA GCP:	South African Good Clinical Practice: Clinical Trial Guidelines
SAHPRA:	South African Health Products Regulatory Authority
SANCTR:	South African National Clinical Trials Register
SOP:	Standard Operating Procedure
Sub-I:	Sub-Investigator
TCAMS:	Traditional, Complementary and Alternative Medicines (TCAMS)
TIE:	Time, Inconvenience and Expenses
TMF:	Trial Master File
WHO:	World Health Organisation

1. INTRODUCTION

The optimal methodology by which to test and evaluate new treatments, medicines, interventions and devices is a carefully designed scientifically sound and ethical clinical trial. The underlying principle is that advances in health care knowledge are dependent on contributions from human participants, researchers and sponsors. However, achievement of scientific goals is balanced against respect for and protection of the interests of human research participants and researchers. Thus, clinical trials are acceptable only when they are ethical and safe both in design and the way they are conducted.

The ethical considerations that inform the design of an ethical clinical trial are largely the same considerations that inform ethical health research more generally. Nevertheless, aspects of clinical trials require special consideration, which necessitates explicit deliberation on these aspects. Robust Good Clinical Practice (GCP) standards are necessary in addition to the ethical guidelines because clinical trials may have complex trial designs that involve invasive interventions, as well as investigative products and procedures that pose more than minimal risk of harm for participants.

These revised GCP clinical trial guidelines (referred to as SA GCP 2020) have been updated to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting, and to ensure continued adherence to the highest ethical and scientific standards to promote protection of participants and validity of trial results. These guidelines align with the International Council of Harmonisation (ICH) Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R2) 2016 (ICH GCP 2016), and with the Department of Health *Ethics in Health Research Guidelines* 2nd edition 2015 (DoH 2015). It is important for users to familiarise themselves with the clear alignment between DoH 2015 and SA GCP 2020 so that they design, plan, manage and conduct their clinical trials in accordance with the ethical principles and values that underpin their practical application to clinical trials.

All necessary information contained in SA GCP 2006 is included in SA GCP 2020. Some is consolidated, some is revised and updated, and some is reorganised in pursuit of providing user-friendly informative guidelines for conducting clinical trials. Where procedures or principles require explanation or elaboration for the South African context, these are addressed.

1.1 PURPOSE OF THE GUIDELINES

1.1.1 These guidelines have the purpose of providing researchers and other interested parties with clearly articulated standards of GCP in locally conducted research that address the local realities and contexts, to ensure that clinical trials involving South African human participants are designed and conducted according to local requirements as well as according to the sound scientific and ethical standards within the accepted framework for good clinical practice.

- 1.1.2 Compliance with these GCP standards serve to assure the public that the interests, safety and well-being of trial participants are protected and also that clinical trial data are likely to be credible and meaningful.

1.2 SCOPE OF THE GUIDELINES

- 1.2.1 These guidelines focus on design, planning, management, conduct and regulation of clinical trials involving human participants. They do not repeat the ethical principles that underpin sound and ethical research, which are outlined in the Department of Health's *Ethics in Health Research: Principles, Processes and Structures* 2nd edition (2015) (referred to as DoH 2015).

The term 'clinical trial' is inclusive. Specific types of clinical trials are not addressed separately unless a particular need is identified, i.e. 'clinical trials' includes trials involving complementary medicines, African traditional medicines, and non-pharmacological interventions including surgical procedures, medical devices, cell therapy, genetics and genomics, and imaging technology. Consequently, these guidelines, read with DoH 2015, provide guidance for any clinical trial involving human participants, especially those with experimental designs.

- 1.2.2 All role players involved with clinical trials should also be familiar with other national and international guidelines, including but not limited to the following current versions or their successors:
- 1.2.2.1 Department of Health's *Ethics in Health Research: Principles, Processes and Structures* 2nd edition (2015) (referred to as DoH 2015)
 - 1.2.2.2 Declaration of Helsinki (2013)
 - 1.2.2.3 ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R2) 2016 (ICH GCP 2016)
 - 1.2.2.4 ICH Harmonised Tripartite Guideline: Clinical Investigation of Medicinal Products in the Pediatric Population E11 2000
 - 1.2.2.5 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research involving Human Subjects (2016)
 - 1.2.2.6 CIOMS with WHO International Ethical Guidelines for Epidemiological Studies (2009)
 - 1.2.2.7 Clinical Trial Compensation Guidelines, Association of British of Pharmaceutical Industry (ABPI) Guidelines (2014)
 - 1.2.2.8 European Union requirements at http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm
 - 1.2.2.9 World Health Organisation WHO Technical Report Series, No. 850 Guidelines for good clinical practice (GCP) for trials on pharmaceutical products (1995)
 - 1.2.2.10 World Health Organisation Handbook for Good Clinical Research Practice (GCP) (2005)

1.2.2.11 World Health Organisation Good Clinical Laboratory Practice (GCLP) (2009)

1.2.3 In the event of an interpretation conflict between these guidelines (SA GCP 2020) and an international guideline, SA GCP 2020 takes precedence. In the event of a conflict between SA GCP 2020 and a South African legal requirement where both appear to address the same issue or activity, generally, the legal requirement should take precedence, unless an ethical or GCP justification clearly demonstrates otherwise. It is advisable for Research Ethics Committees (RECs) to consult with the National Health Research Ethics Council (NHREC) and/or South African Health Products Regulatory Authority (SAHPRA) about which takes precedence situation to promote standardisation.

1.3 LEGAL STATUS OF THE GUIDELINES

These guidelines are established in terms of Regulations issued in terms of sections 90(s) and 72(6)(c) of the National Health Act, Act No. 61 of 2003 as well as Regulation 30 of the Medicines and Related Substances Act, Act No. 101 of 1965. Compliance with these guidelines is compulsory under the direction of the Director-General of Health.

2. KEY CONCEPTS IN CLINICAL TRIALS

2.1 ETHICAL PRINCIPLES

- 2.1.1 Clinical trials should be conducted in accordance with all the ethical principles outlined in the Declaration of Helsinki, and must be consistent with GCP and other applicable regulatory requirements.
- 2.1.2 Ethical principles of beneficence and non-maleficence, distributive justice (equity) and respect for persons (dignity and autonomy), discussed in detail in 2.1 of DoH 2015, govern all clinical trials conducted in South Africa.

2.2 JUSTIFICATION FOR TRIAL

In preparing for a clinical trial, the specific aims, challenges and the risk of harm and the likelihood of benefit of the trial must be thoroughly considered. The chosen design and methodology must be scientifically sound and ethically justified.

2.3 RISK, BURDENS AND BENEFITS

- 2.3.1 All research involving human participants must be scrutinised to assess the potential risk of harm. Clinical trials should be initiated and continued only if the importance of the objective and anticipated benefits outweighs the potential risks and burdens for the trial participants. The ratio of risk of harm to likelihood of benefit must be assessed as part of the review process before the trial begins. The assessment should take full cognisance of possible benefits and harms beyond the life of the trial itself, particularly in the case of chronic life-threatening conditions.
- 2.3.2 A favourable ratio is one where, at minimum, the potential risk of harm to a participant is outweighed by the likelihood of benefit, to participants directly or to society in future, from the knowledge to be gained from the research. When making this assessment, both the magnitude of the harm and the probability of its occurrence should be addressed.
- 2.3.3 Foreseeable harm (anticipated negative side effects) must be described clearly to enable RECs to understand and evaluate them against potential benefits that may result from the trial.
- 2.3.4 Potential participants must be informed of potential risks of harm to enable them to make an informed decision about whether to participate in the trial.
- 2.3.5 Researchers must supply information about the outcomes of previous pre-clinical and clinical research on the investigational intervention and must justify the further research using the intervention.
- 2.3.6 Research involving human participants who might face high risk of harm should only be approved after careful review and acceptable justification that demonstrates the potential importance and value of the research for society. A carefully phased approach should be adopted in such cases and appropriate harm mitigating measures must be put into place.

2.4 RIGHTS AND SAFETY OF PARTICIPANTS

- 2.4.1 The rights, safety and well-being of trial participants are the most important considerations and should prevail over interests of science and society.
- 2.4.2 The local Principal Investigator (PI) has, or the Co-Principal Investigators (Co-PI) have, primary responsibility for the safety and welfare of local participants.
- 2.4.3 Confidentiality of records, including electronic, that could identify participants must be maintained and access to records must be managed responsibly.
- 2.4.4 Participants' right to privacy must be protected, e.g. by using appropriate precautions to avoid identification or recognition of participants.
- 2.4.5 Systems with procedures that assure the quality of every aspect of the trial should be implemented. Aspects of the trial that are essential to ensure human participants protection and reliability of trial results should be the focus of such systems.

2.5 INFORMED CONSENT

- 2.5.1 Freely given informed consent must be obtained from every participant prior to clinical trial participation.

NOTE: Where proposed participants are incapable of providing consent e.g. because of loss of consciousness, different procedures may apply; see 3.2.4.3 of DoH 2015.

- 2.5.2 Informed consent documentation and procedures for multi-site and multi-country trials must be sensitive to country- and site-specific requirements. The site PI must ensure that the informed consent content and procedures are tailored accordingly.
- 2.5.3 The informed consent documentation must be approved by the REC before implementation. The approved written Informed Consent should be signed and witnessed as applicable.
- 2.5.4 In clinical trials involving minors, prior documented parental permission to approach the minor to invite participation must be obtained before approaching the minor. The minor chooses whether to participate and provides assent to indicate an affirmative answer. See 3.1.9 and 3.2.2 of DoH 2015 for detailed information on informed consent and minors, including how to manage situations where the minors do not have parents or guardians.

2.6 ETHICS REVIEW

- 2.6.1 All clinical trials involving human participants must undergo an independent ethical review. The REC which undertakes the review must be registered with the NHREC.
- 2.6.2 A registered REC must review and approve the protocol and associated documentation before any trial may begin, in accordance with 1.6 DoH 2015.
- 2.6.3 The following aspects must be addressed explicitly:

- 2.6.3.1 The scientific merit of the clinical trial.
- 2.6.3.2 Social merit of the clinical trial in light of South Africa's research priorities.

NOTE: If the topic for investigation is not high on the research priority list, the research may still be conducted subject to appropriate justification for doing the work.

- 2.6.3.3 Whether and why randomization is relevant, and how this is addressed.
- 2.6.3.4 The appropriateness of the inclusion/exclusion criteria for the South African context.
- 2.6.3.5 The appropriateness of the recruitment process for the South African context.
- 2.6.3.6 The feasibility of obtaining meaningful results with the lowest possible risk of harm for participants.
- 2.6.3.7 Whether the risk of harm is appropriately weighed against anticipated benefits for participants or the class of persons from which they are drawn.¹
- 2.6.3.8 High risk of harm may be justifiable where the anticipated benefit is of high importance to increase relevant knowledge and appropriate mitigating measures are in place to minimise harm to participants.

NOTE: Attention must be given to harms and benefits beyond the life of the trial itself, especially in respect of early phase studies and (pharmacovigilance) surveillance for chronic and life-threatening conditions. The proposal must explain what trigger alerts will be in place. Clear guidance for participants about post-trial care must be provided.

2.7 TRIAL INCENTIVES AND PARTICIPANT REIMBURSEMENT

- 2.7.1 Using incentives to attract potential participants needs careful consideration. Incentives should not cause a person to ignore, minimise or undervalue the risks posed by the trial. See 3.1.7 DoH 2015 guidelines for more details.
- 2.7.2 The informed consent process should ensure that potential participants grasp the important considerations like the potential risk of harm and that they do not focus on incentives when thinking about whether to participate.
- 2.7.3 However, paternalism must be avoided. If a clinical trial has been approved on the basis that it is ethical including having a reasonable risk/benefit ratio, then no principled objection to persons choosing to participate should exist.
- 2.7.4 Reimbursement or payment of participants' expenses is not an incentive. Costs of transport and refreshments should be provided by the trial.

¹ See DoH 2015 2.3.4 for details; the PI is responsible for assessing the risk of harm; the REC may require additional protections if the risk of harm warrants it.

2.7.5 A fair rate of reimbursement should be calculated using the Time, Inconvenience and Expenses (TIE) method² to determine the cost to participants for time expended, inconvenience and refreshments associated with research participation. This method costs expenses at the current hourly rate for unskilled labour in the marketplace, regardless of whether the participant is employed. It should be noted that no *prescribed* reimbursement amount prevails in SA (see the document cited in footnote 2).

2.8 SCIENTIFIC REQUIREMENTS FOR RESEARCH PROTOCOLS

2.8.1 Clinical trials should be scientifically sound and be based on a thorough knowledge of the scientific literature, other relevant sources of information, as well as adequate laboratory and, if appropriate, ethical animal experimentation.

2.8.2 The available pre-clinical and clinical information on an investigational product (IP) should be adequate to support the proposed clinical trial.

2.8.3 Clinical trials should be described in a clear, detailed protocol.

2.9 DATA MANAGEMENT AND DISSEMINATION OF RESEARCH RESULTS

2.9.1 All clinical trial information should be recorded, managed and stored to permit accurate reporting, analysis, interpretation and verification.

2.9.2 This principle applies to all records referenced in this guideline, regardless of the nature of the medium of record.

2.9.3 PIs are ethically obliged to ensure the reporting of a clinical trial's existence and the findings obtained.

2.9.4 PIs must report and disseminate research results or findings in a timely, accessible, responsible and competent manner. This includes providing feedback to participant communities where appropriate, in accordance with the principle of role player engagement and collaboration.

² NHREC 2012 'Payment of trial participants in SA: ethical considerations for research ethics committees' (available at <http://nhrec.health.gov.za>; also at <https://sahpra.org.za>).

3. MANAGING RECRUITMENT OF VULNERABLE PARTICIPANTS

3.1 FACTORS CONTRIBUTING TO VULNERABILITY

- 3.1.1 External circumstances like low levels of literacy and formal education, advanced age, young age, personal and socio-economic circumstances, including significant poverty and poor access to health care, may increase vulnerability of South Africans (see 3.2 of DoH 2015 for detailed discussion).
- 3.1.2 Certain groups of persons are vulnerable due to diminished health, loss of liberty or other health-related personal circumstances, including adults with diminished decisional capacity, persons with mental illness, mental disability, or persons who have substance abuse problems, persons in dependent relationships, incarcerated offenders and persons highly dependent on medical care.
- 3.1.3 Vulnerable persons should not be recruited merely because they are conveniently accessible if the research could be conducted with less vulnerable participants.
- 3.1.4 The research for which vulnerable persons are to be recruited should be relevant to the health needs and priorities of their communities or groupings.
- 3.1.5 RECs may impose additional measures to protect the welfare of vulnerable participants. For example, they may impose additional protective measures for the informed consent process, or require increased monitoring and interim reporting on the participants' welfare.

3.2 MINORS

- 3.2.1 Minors (younger than 18 years) are regarded as vulnerable persons due to their lack of legal capacity (See 3.2.2 of DoH 2015 for detailed discussion).
- 3.2.2 Minors should participate in research only where their participation is indispensable to the research, i.e. the research cannot deliver the desired outcomes if adult participants were to be used instead (see 3.2.2.1 of DoH 2015).
- 3.2.3 RECs must note that clinical trial research is regarded as 'non-therapeutic' in terms of the legal framework. 'Non-therapeutic research' means research that includes interventions that will not hold out the prospect of direct health-related benefit for the participant but may produce results that contribute to generalisable knowledge (NHA 61 of 2003, Regulation 135 of 2012).
- 3.2.4 'Non-therapeutic' research with minors requires Ministerial consent per Form A in the above-mentioned Regulations (to be completed by the applicant). The REC must ensure that its deliberations on the specified requirements for inclusion of minors as participants are properly minuted and recorded as required by the Regulations. The membership of the REC must include appropriate paediatric research expertise.
- 3.2.5 Consent requirements for minors: For research purposes, the following should be obtained:

- 3.2.5.1 Documented permission and/or consent from a parent or legal guardian in accordance with ss 10 and 31 of the Children's Act 38 of 2005 (see also 3.2.2.4 of DoH 2015).
- 3.2.5.2 Assent from the minor in writing where he/she is capable of understanding.
- 3.2.5.3 A child's refusal to participate in research must be respected.
- 3.2.6 Orphans without court appointed guardians may participate in clinical research when the minimum conditions of research (discussed in more detail in 3.2.2.3 of DoH 2015) are satisfied. In such cases, a parental substitute should be used to provide written consent. The parental substitutes should be used in descending order as listed in this paragraph of DoH 2015.

3.3 ADULTS WITH FACTUAL INCAPACITY TO PROVIDE INFORMED CONSENT

Adults who are factually incapable of giving informed consent should participate in research only when their participation is indispensable to research. In such cases proxy consent may be appropriate as detailed in 3.2.4 of DoH 2015.

3.4 PERSONS IN DEPENDENT RELATIONSHIPS OR COMPARABLE SITUATIONS

- 3.4.1 Particular attention should be given to ensuring that participants are adequately informed and can choose voluntarily whether to participate in research.
- 3.4.2 This group includes persons in junior or subordinate positions of hierarchically structured groups and may include but is not limited to the following:
 - 3.4.2.1 Relationships between older persons and their caregivers;
 - 3.4.2.2 Persons with chronic conditions or disabilities and their caregivers;
 - 3.4.2.3 Persons with life-threatening illnesses;
 - 3.4.2.4 Patient and health care professionals;
 - 3.4.2.5 Employees and employers;
 - 3.4.2.6 Members of the uniformed services;
 - 3.4.2.7 Incarcerated offenders;
 - 3.4.2.8 Wards of the state and guardians;
 - 3.4.2.9 Students and teachers (including university lecturers); and
 - 3.4.2.10 Relatives of the research team.

4. REGULATORY AUTHORITIES' ROLES AND RESPONSIBILITIES

4.1 NATIONAL HEALTH RESEARCH ETHICS COUNCIL (NHREC)

The NHREC is the national statutory body established in terms of the National Health Act (NHA). The NHREC's core responsibilities are to advise the Minister of Health, to set ethical norms and standards for health research, including clinical trials, and to advance research ethics in South Africa by promoting compliance by researchers and RECs using existing and new regulations and guidelines.

The NHREC is mandated to register and audit RECs. In addition, the NHREC has responsibility for adjudicating complaints, and for advising institutional committees, researchers, members of the public, and national and provincial departments of health on ethical matters concerning research.

This body reports to the Minister of Health and is supported by the Secretariat of the Research Directorate of the Department of Health.

4.2 SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY (SAHPRA)

SAHPRA is a statutory body established in 2018 in terms of the Medicines and Related Substances Act 101 of 1965 (the "Medicines Act") for the purpose to provide for the monitoring, evaluation, regulation, investigation, inspection, registration and control of health products, including medicines, scheduled substances, medical devices, in vitro diagnostics, clinical trials and related matters in the public interest. SAHPRA must:

- 4.2.1 Ensure efficient, effective and ethical evaluation or assessment of health products that meet defined standards of quality, safety, efficacy and performance, where applicable;
- 4.2.2 Ensure that the process of evaluating or assessing and registering health products is transparent, fair, objective and concluded timeously;
- 4.2.3 Ensure periodic re-evaluation or re-assessment and monitoring of health products;
- 4.2.4 Conduct announced and unannounced inspections.

4.3 RESEARCH ETHICS COMMITTEES (RECs)

4.3.1 The primary responsibility of RECs in South Africa is to ensure that all proposals to conduct health research involving human participants undergo rigorous independent ethics review. This responsibility is exercised to protect the research participants and to ensure that their rights, safety and well-being are respected and protected.

4.3.2 The REC may approve, require amendment to, or reject a research proposal on ethical and/or scientific grounds. The REC must record its feedback in writing and should include, where appropriate, reasons for rejection. The REC's feedback should be structured to be instructive for the investigators concerned.

- 4.3.3 The REC should have the following documents for each application for ethics review:
- 4.3.3.1 Clinical trial protocol(s)/amendment(s);
 - 4.3.3.2 All documents and other material to be used to inform potential participants, including plain-language information sheets, informed consent forms, questionnaires, advertisements and letters;
 - 4.3.3.3 Investigator's Brochure (IB);
 - 4.3.3.4 Any other additional safety, quality and/or efficacy information;
 - 4.3.3.5 Amount and sources, or potential sources, of funding for the clinical trial;
 - 4.3.3.6 Information about incentives or reimbursements available to participants;³
 - 4.3.3.7 Declaration of any affiliation and/or potential conflict of interest;
 - 4.3.3.8 The investigator's current curriculum vitae (CV) and any other documentation evidencing suitable qualifications and experience;
 - 4.3.3.9 Evidence that the investigator has sufficient time to oversee the research project;⁴
 - 4.3.3.10 Evidence of current (i.e. within three years) GCP training as well as general research ethics training. Basic GCP training must be done by means of attendance at a face-to-face course and must include specific SA GCP 2020 training. Thereafter, three-yearly refresher GCP training must occur. Refresher training may be done online; however, the course must be relevant to the South African research environment and must include SA GCP 2020 training.
- NOTE: Trial staff whose GCP training has expired for more than three months must re-do the basic GCP course.*
- 4.3.3.11 Any other documentation that the REC may need to fulfil its responsibility, such as documents that address ethical concerns of a proposed research project.
- 4.3.4 Requirements of membership of REC are covered in detail in 4.4.1 of DoH 2015.
- 4.3.4.1 The membership should include as many disciplines, sectors and professions as possible, appropriate to the research under review.
 - 4.3.2.2 REC members who review clinical trial proposals should have research ethics training and GCP training, evidenced by certificates issued not more than three years previously.
- 4.3.5 The REC should have written standard operating procedures (SOPs) as per 4.5 of DoH 2015.

³ See note 2 above.

⁴ For example, the investigator must declare how many open trials he or she currently oversees; this gives an idea of whether sufficient time is likely to be available or whether the investigator is overcommitted. It may be regarded as unethical conduct when the investigator is overcommitted so that appropriate attention is not available for a trial.

4.3.6 The REC 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 three years or as per institutional requirement, whichever period is longer, after completion of the trial and make them available upon request from the applicable regulatory authority.

4.4 SOUTH AFRICAN NATIONAL CLINICAL TRIALS REGISTER (SANCTR)

The Department of Health has established the SANCTR, a web-based publicly accessible clinical trial register (www.sanctr.gov.za). Sponsors/Applicants must register all South Africa-based trials on the SANCTR. If there is no Sponsor, the PI must register the trial. Entry of the SAHPRA and REC approvals triggers allocation of a unique study number for each trial. No trial may commence without this DoH number.

The SANCTR is intended to:

- 4.4.1. Promote collaboration among researchers in both the public and private health care sectors through sharing research information;
- 4.4.2 Inform the public to assist people to identify clinical trials for possible participation;
- 4.4.3 Reduce duplication of research efforts; and
- 4.4.4 Promote best use of limited research resources.

NOTE: Registration with SANCTR does not equate with SAHPRA or ethics approval, both of which are essential to obtain BEFORE a trial begins. Usually SAHPRA and ethics review applications are submitted simultaneously to expedite matters.

4.5 NATIONAL HEALTH RESEARCH COMMITTEE (NHRC)

The NHRC is the national statutory body responsible for determining the nature, scope, as well as the co-ordination of health research carried out by public health authorities. Its mandate is to ensure that priority health problems and needs receive appropriate attention and resources, and to advise the Minister of Health on implementation of an integrated national strategy for health research. In identifying priorities, the NHRC takes into account the burden of disease, the cost-effectiveness of interventions to address the burden of disease, the resource implications (especially at the lowest levels of health care delivery), and the health needs of vulnerable persons including women, older persons, children and persons with disabilities. Where appropriate, health needs of whole communities must also be considered.

4.6 PROVINCIAL HEALTH RESEARCH COMMITTEES (PHRC)

The PHRC collects and transmits information about local health needs and resource constraints to the NHRC. They are gatekeepers for public health care delivery sites.

NOTE: Only PHRC's that are registered with NHREC may also do ethics review of protocols.

5. INVESTIGATOR

5.1 CATEGORIES OF INVESTIGATOR

- 5.1.1 In most cases, clinical trials are conducted by an Investigator who has entered into an agreement with a Sponsor to conduct a clinical trial. She or he is the person responsible for the conduct of the clinical trial at the trial site(s). In the case of a multi-centre trial, each site must have a local PI and at least one sub-investigator (Sub-I) who are registered with the Health Professions Council of South Africa (HPCSA). It is unacceptable to have an 'absentee' PI.
- 5.1.2 The **PI** must be a South Africa-based clinician and must have actively participated in at least two clinical trials as a sub-investigator. The local PI has sole or joint responsibility for the conduct of trial and delegation of trial responsibilities of the trial.
- 5.1.3 A **Sub-I** must be a South Africa-based member of the clinical team designated and supervised by the PI at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions.
- 5.1.4 A **Co-PI** may be included and may be a qualified non-clinician South Africa-based scientist; e.g. a laboratory/medical scientist, pharmacologist, pharmacist, dentist or equivalent qualified and experienced person who can provide trial oversight management. At least one Co-PI must be a clinician and qualified to provide medical oversight. A Co-PI must meet all the requirements to be a PI. The role of each Co-PI must be clearly described for the trial and their complementary responsibilities carefully detailed so that all responsibilities of the PI, as defined, are covered. While both Co-PIs have defined roles and functions in relation to the conduct of the trial, in terms of legal responsibility, they will be jointly and severally liable.
- 5.1.5 For multi-centre studies in South Africa, a National Principal Investigator (**NPI**), with expertise and experience in the relevant field, may be appointed to take overall responsibility for the conduct of a trial. The NPI must meet all requirements to be a PI, must sign a declaration accepting responsibility and must sign off the SAHPRA clinical trial form (CTF1) application, co-ordinate concerns of investigators regarding conduct of trial and communicate these to the Sponsor/Applicant, RECs and SAHPRA, as necessary. It is recommended that the NPI should be involved as an investigator at one of the trial sites.

NOTE: Trials using African Traditional Medicine as well as other Traditional, Complementary and Alternative Medicines (TCAMS) may have a Co-PI (non-clinical) with appropriate expertise, together with a clinically qualified Co-PI.

- 5.1.6 If the PI and/or Sub-I withdraw(s) for any reason (including death) before completion of the study, a suitably qualified successor should be appointed by the Sponsor, and approved by SAHPRA and the relevant REC, to take over responsibility for conducting the trial.

5.2 INVESTIGATOR QUALIFICATIONS AND AGREEMENTS

The Investigator must:

- 5.2.1 Be qualified by education, training and experience to assume responsibility for the proper conduct of the trial, and must meet all the qualifications specified by the South African regulatory requirements and provide evidence of such qualifications through a current CV and other relevant documentation requested by the Sponsor/Applicant, the RECs, and/or SAHPRA.
- 5.2.2 Be thoroughly familiar with the appropriate use of the IP, as described in the protocol, in the current IB, in the product information and/or in other information sources provided by the Sponsor.
- 5.2.3 Comply with GCP and other applicable regulatory requirements, including registration of the clinical trial with the SANCTR and reporting of Serious Adverse Events (SAEs) to the RECs and SAHPRA.
- 5.2.4 Permit monitoring and auditing by the Sponsor, and inspection by South African and other appropriate regulatory authorities.
- 5.2.5 Maintain a list of appropriately qualified persons to whom he/she has delegated significant trial-related duties.

5.3 ADEQUATE RESOURCES

The Investigator must:

- 5.3.1 Demonstrate (e.g. based on retrospective data) the potential to recruit the required number of suitable participants within the agreed recruitment period.
- 5.3.2 Have sufficient time to properly conduct and complete the trial within the agreed trial period.
- 5.3.3 Have available an adequate number of appropriately qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- 5.3.4 Ensure that all persons assisting with the trial are adequately informed about the protocol, the IP and their trial-related duties and functions.
- 5.3.5 Be responsible for supervising any individual or party to whom the Investigator delegates study tasks conducted at the trial site.
- 5.3.6 Ensure that any party retained to perform study tasks is qualified to perform those study tasks.
- 5.3.7 Implement procedures to ensure the integrity of performance of the study tasks performed and any data generated.

5.4 MEDICAL CARE OF TRIAL PARTICIPANTS

- 5.4.1 A qualified clinician, who may be the PI, Co-PI or, if appropriate, a Sub-I, must be responsible for all trial-related medical decisions.

- 5.4.2 The Investigator must ensure that adequate medical care is provided to a participant for any adverse events (AEs), including clinically significant laboratory values, related to the trial.
- 5.4.3 The Investigator must inform a participant when medical care is needed for intercurrent illness of which the Investigator becomes aware.
- 5.4.4 At all times the participant's clinical interests must take precedence.
- 5.4.5 It is recommended that the Investigator should advise the participant to inform his/her primary health care provider as well as any other healthcare provider he/she may see about his/her participation in the trial. Alternatively, the participant may give permission to the Investigator to perform this task.
- 5.4.6 A participant is not obliged to give reasons for deciding to withdraw from a trial prematurely. However, to collate clinical trial information, the Investigator should make a reasonable effort to ascertain the reason, while fully respecting the participant's right to decline to disclose.

5.5 COMMUNICATION WITH REC AND/OR SAHPRA

- 5.5.1 Prior to initiating a clinical trial, the Investigator must have written and dated regulatory and ethics approval for the research protocol, written informed consent form, consent form updates, participants recruitment procedures (e.g. advertisements), and other related documents from the REC and, if appropriate, from SAHPRA.
- 5.5.2 During the clinical trial, the Investigator must provide the REC and/or SAHPRA (if appropriate) with all updated documents, including but not limited to, updated IB, additional safety data, updated informed consent and protocol amendments.
- 5.5.3 The Investigator must provide regular REC (at least annually) and SAHPRA (at least six-monthly) progress reports.

5.6 COMPLIANCE WITH THE PROTOCOL

The Investigator:

- 5.6.1 Must conduct the trial in compliance with the protocol agreed to with the Sponsor and approved by the REC and/or SAHPRA. The Investigator and the Sponsor must sign the protocol to confirm agreement.
- 5.6.2 May not implement any deviation from or changes to the protocol without agreement by the Sponsor and further review and documented approval from the REC and SAHPRA of the amendment, except where necessary to eliminate an immediate hazard to trial participants, or when the change involves only logistical or administrative aspects of the trial (e.g. change in monitors, change of telephone number).
- 5.6.3 May implement a deviation from or a change to the protocol in order to eliminate an immediate hazard to trial participants. As soon as possible, the exceptional implemented deviation or change, the reasons for it and, if

appropriate, the proposed protocol amendment(s) should be documented and submitted to:

- (a) the REC for review and approval,
- (b) the Sponsor for agreement, and/or
- (c) SAHPRA.

5.6.4 Should document and explain any deviation from the approved protocol.

5.7 INVESTIGATIONAL PRODUCTS

- 5.7.1 Responsibility for IP accountability at a trial site rests with the Investigator.
- 5.7.2 Where allowed/required, the Investigator may assign some of his/her duties for IP accountability at a trial site to an appropriate pharmacist or another appropriate individual under the supervision of the Investigator.
- 5.7.3 Only a clinician with a dispensing license and/or an approved pharmacist may dispense IP at a trial site.
- 5.7.4 IP may be imported into South Africa only after approval of the protocol by SAHPRA. Samples of the IP to be imported before trial approval require a section 21 permit from SAHPRA.
- 5.7.5 The investigator and/or pharmacist or other appropriate individual, must maintain records of the IP's delivery to the trial site, inventory at the site, use by each participant and return of unused product to the Sponsor or alternative disposition thereof. These records must include dates, quantities, batch/serial numbers, expiry dates (if applicable) and the unique code numbers assigned to the IP and trial participants, as appropriate. The Investigator must maintain records that document adequately that the participants were provided the doses specified by the protocol and must reconcile all IP received from the Sponsor.
- 5.7.6 The IP must be stored as specified by the Sponsor, and in line with Good Pharmacy Practice (GPP) and Good Manufacturing Practice (GMP) in South Africa, SAHPRA regulations and conditions.
- 5.7.7 All unused IP of a trial must be disposed of in line with the protocol approved by SAHPRA.
- 5.7.8 The Investigator must ensure that the IP is used only in accordance with the approved protocol.
- 5.7.9 The Investigator, or the appropriate designee, must explain the correct use of the IP to each participant and should check, at intervals appropriate for the trial, that each participant is following the instructions properly.

5.8 RANDOMIZATION PROCEDURES AND UNBLINDING

- 5.8.1 The Investigator must follow the trial's randomization procedures, if any.
- 5.8.2 In blinded studies, the protocol must specify the circumstances under which the code may be broken and the procedure for unblinding.

- 5.8.3 Any premature unblinding of the IP for whatever reason (e.g. accidental unblinding or due to a SAE) should be documented and promptly explained to the Sponsor.

5.9 INFORMED CONSENT FOR CLINICAL TRIAL PARTICIPANTS

- 5.9.1. The Investigator is responsible for ensuring that an adequate information package, in an acceptable format appropriate for the South African context, is available for use in the process of seeking informed consent from participants to participate in the clinical trial (as described in 3.1 of DoH 2015).
- 5.9.2 If the trial is a multi-site and/or multi-country trial, 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.
- 5.9.3 All recruitment and informed consent documentation must be reviewed and approved by the REC before implementation in the trial.
- 5.9.4 Written informed consent documentation and other participant-related information should be revised when new information that may be relevant to consent or to willingness to continue to participate in the trial becomes available. Any revisions must be submitted for ethics review and approval before implementation. Communication of the new information to participants must be documented.
- 5.9.5 The Investigator or the trial recruitment staff must not coerce or unduly influence a participant to participate or to continue to participate in a trial.
- 5.9.6 No information concerning the trial, including written informed consent documents, should cause a participant to waive or to appear to waive legal rights, or to release the Investigator, the Sponsor or their agents from liability for negligence.
- 5.9.7 The language of the informed consent document should be non-technical and understandable to the participant or the impartial witness, where applicable.
- 5.9.8 The informed consent document should be provided in a participant's preferred written language.
- 5.9.9 Participants must be given sufficient time to consider, to consult and to ask questions about the trial before being asked to choose whether to participate. All questions must be answered appropriately to the satisfaction of the participant.
- 5.9.10 Participants and the person who conducted the informed consent discussion must personally sign and date the consent document.
- 5.9.11 When participants can be enrolled only with assistance of the participant's legally acceptable representative (e.g., minors or persons with factual decision-making incapacity), the participant should nevertheless be informed about the trial to the extent compatible with the participant's understanding

and, if capable, the participant should sign and personally date the written informed consent.

- 5.9.12 Where the participant or the legally acceptable representative is illiterate, verbal consent should be obtained in the presence of an impartial witness. The participant should indicate willingness to participate by making a mark (either a cross or a finger print). The witness signs to affirm that the participant willingly consented to participate. The witness dates the mark and his/her signature.
- 5.9.13 The consent discussion and documentation must explain to potential participants:
- (a) That the trial involves research;
 - (b) The purpose of the trial;
 - (c) Why the potential participant has been approached;
 - (d) That participation is voluntary; that refusal to participate, or withdrawal from the trial at any time, will not prejudice the ongoing care of the person in any way;
 - (e) That access to trial IP may be randomly assigned and what the probability for random assignment to each arm is (where appropriate);
 - (f) How trial procedures are to be followed, including all invasive procedures;
 - (g) The nature of a participant's responsibilities;
 - (h) Those aspects of the trial that are experimental;
 - (i) The foreseeable risks of harm or inconvenience to the participant and, when applicable, to an embryo, foetus or nursing infant;
 - (j) The probability and magnitude of the foreseeable risks of harm;
 - (k) The expected benefits. When no anticipated clinical benefit to a participant is anticipated, the participant must be made aware of this (e.g. Phase I Clinical Trial);
 - (l) The alternative procedure(s) or course(s) of treatment that may be available to the participant, and their important potential benefits and risks;
 - (m) The compensation and/or medical treatment available to the participant in the event of trial-related injury;
 - (n) The planned incentives, if any, to attract the participant;
 - (o) The planned reimbursements, if any, for time, inconvenience and expenses;
 - (p) That participant records may be accessible to Sponsor/Applicant, SAHPRA, NHREC, relevant REC and/or other regulatory authorities;
 - (q) The identity of the person(s) to contact for trial-related queries and injuries;
 - (r) REC contact details for information and concerns regarding the rights of trial participants;
 - (s) The identity of the Sponsor;
 - (t) Potential conflict of interest (COI) of the PI;

- (u) That trial records including those that identify participants are kept confidential within the bounds of the law;
- (v) The expected duration of participation;
- (w) The foreseeable circumstances and/or reasons that may lead to the participant's participation in the trial being stopped;
- (x) The planned number of participants locally and globally involved in the trial;
- (y) That new information that may affect the willingness of participants to continue participation in the trial will be made available timeously to the participant.

5.9.14 The Investigator, or an appropriate designee, should obtain the participant's consent to participate in the trial in accordance with the principles outlined in DoH 2015, the Declaration of Helsinki and other guidelines.

5.9.15 When prior consent of the participant is not possible, the consent of the participant's legally acceptable representative, if present, should be requested. When prior consent of the participant is not possible, and the participant's legally acceptable representative is not available, enrolment of the participant should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the REC, to protect the rights, safety and well-being of the participant and to ensure compliance with applicable regulatory requirements. The participant or the participant's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested (see also 3.4 of DoH 2015).

5.9.16 Once informed consent has been obtained, the original signed informed consent document must be kept with the trial records, and a copy of the signed informed consent document must be offered to the participant. A further copy of the signed informed consent document must be in the participant's source documents or medical records.

5.10 RECORDS AND REPORTS

5.10.1 The Investigator is responsible for collection, quality, recording, maintenance and retrieval of source data arising from the clinical study.

5.10.1.1 The Investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants.

5.10.1.2 Source documents should adhere to the ALCOA-CCEA standard (attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available).

5.10.1.3 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 stored securely.

- 5.10.1.4 Changes to source data must be traceable, must not obscure or delete the original entry, and must be explained if necessary (e.g. via an audit trail).
- 5.10.2 The Investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the Sponsor by means of Case Report Forms (CRF). The design of the CRF should facilitate observation of the participant and be consistent with the study protocol.
 - 5.10.2.1 The protocol should specify which data will be entered directly into the CRF and will not be supported by other source data.
 - 5.10.2.2 Corrections to CRFs may be made only by the Investigator or an appropriate designee.
 - 5.10.2.3 Changes to CRFs must be traceable, must not obscure or delete the original entry, and must be explained if necessary (e.g. via an audit trail).
- 5.10.3 Data collected by direct entry on a computer should be entered only by the Investigator and/or an appropriate designee.
 - 5.10.3.1 The computer system must be virus-proofed, access-restricted and must record a data trail of all changes made to CRFs.
 - 5.10.3.2 The system should be designed so that data changes are documented automatically, and so that no deletion of entered data can occur in order to maintain, audit and edit the data trail.
 - 5.10.3.3 Once a hard copy of the computer stored data has been made, procedures for editing are as for paper CRF.
- 5.10.4 The Investigator should maintain the trial documents as specified in the Essential Documents for the Conduct of a Clinical Trial (see Section 9 below). The Investigator must take measures to prevent accidental and/or premature destruction of these documents.
- 5.10.5 Essential documents must be retained for at least 10 years after final closure of clinical trial or for at least two years after formal discontinuation of clinical development of the IP.
- 5.10.6 A clinical trial agreement (CTA) must be signed by the Sponsor/Applicant and the Investigator.
 - 5.10.6.1 Financial aspects of the clinical trial must be documented in the CTA.
 - 5.10.6.2 The CTA must also describe in detail the responsibilities of the Sponsor/Applicant and Investigator.
- 5.10.7 Upon request, the Investigator must make the data available for direct access by the Sponsor/Applicant to enable conduct of data editing and audit in accordance with the protocol and/or CTA.

5.11 PROGRESS REPORTS

- 5.11.1 The Investigator must submit written summaries of trial status to:
 - (a) The REC annually, or more frequently as requested; and
 - (b) SAHPRA every six months, or more frequently as requested.

- 5.11.2 This information should include but not be limited to:
- 5.11.2.1 Progress to date, or the outcome in the case of completed research;
 - 5.11.2.2 Current enrolment status (numbers, active or closed);
 - 5.11.2.3 Whether participant follow-up is still active or has been completed;
 - 5.11.2.4 Evidence of non-compliance with the approved protocol or any conditions of approval;
 - 5.11.2.5 Relevant safety data.
- 5.11.3 The Investigator should promptly provide written reports to the Sponsor/Applicant, the REC and, where applicable, the Institution on any changes that significantly affect conducting the trial and/or that increase the risk of harm to participants.

5.12 SAFETY REPORTING

- 5.12.1 The Investigator must inform the Sponsor/Applicant immediately upon becoming aware of any serious and/or unexpected AEs that occur during the trial, unless identified as unnecessary to report immediately by the protocol and/or another document (e.g. the IB).
- 5.12.2 AEs and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the Sponsor/Applicant in accordance with the reporting requirement and within the time periods specified in the protocol.
- 5.12.3 In the case of participant deaths, the PI must supply the Sponsor/Applicant, the REC and SAHPRA with any additional information as requested.
- 5.12.4 The initial and follow-up reports must identify the affected participants by the participant identification code.
- 5.12.5 The initial serious adverse event report form and any relevant follow-up information must be sent to the Sponsor/Applicant, who in turn must forward the relevant information to SAHPRA.

5.13 PREMATURE TERMINATION OR SUSPENSION OF A CLINICAL TRIAL

- 5.13.1 If a trial is prematurely terminated or suspended for any reason, the Investigator must promptly inform the trial participants, and must ensure appropriate therapy and follow-up for them.
- 5.13.2 If the Investigator terminates or suspends a trial without the prior agreement of the Sponsor, the Investigator must promptly inform the Institution (where applicable), the Sponsor, SAHPRA and the REC, and must provide a detailed written explanation for the termination or suspension.
- 5.13.3 If the Sponsor terminates or suspends a trial, the Investigator must promptly inform the Institution (where applicable), SAHPRA and the REC, and must provide a detailed written explanation for the termination or suspension.

5.13.4 If the REC terminates or suspends a trial, the Investigator must promptly inform the Institution (where applicable), SAHPRA and the Sponsor/Applicant, and must provide a detailed written explanation for the termination or suspension.

5.13.5 If SAHPRA and/or other regulatory authority terminates or suspends a trial, the Investigator must promptly inform the Institution (where applicable), the REC, and must provide a detailed written explanation for the termination or suspension.

5.14 FINAL REPORT

Upon completion of the trial, the Investigator must inform the Institution (if applicable), the REC and SAHPRA and must provide them with a summary of the trial outcome and other required reports.

6. SPONSOR

A **Sponsor** is the person or organisation responsible for the initiation, management or financing of a clinical trial. A Sponsor can be a pharmaceutical company, the PI, a funding body, or an individual or organisation designated by the funding body or academic institution.

It is important that the Sponsor's roles and responsibilities are clearly articulated in the protocol and related documents. (For a description of the roles and responsibilities of the Sponsor for conducting clinical trials in South Africa, see 6.2 below).

A clinical trial can be conducted with or without a Sponsor. If a Sponsor is involved, both the Sponsor and the PI should collaborate to design, conduct and report the trial and its results. If there is no Sponsor, the PI must state clearly in the protocol who takes on the role of the Sponsor in the initiation, management and funding of the trial.

An **Applicant** can be an individual, company, institution, or organisation that acts on behalf of the Sponsor to initiate and manage the trial as its local representative. In the case of an international Sponsor, a local Applicant designated by the Sponsor is responsible for initiation and management of the trial in the local context.

The Sponsor may delegate some of its responsibilities to a Contract Research Organisation (CRO), which should be clearly documented. The Sponsor and Applicant remain responsible for oversight of the conduct and monitoring of the trial.

NOTE: All references to the Sponsor in this guideline also apply to an Applicant or CRO to the extent that the Applicant/CRO has assumed trial-related duties and responsibility of the Sponsor (see section 6.3.4 below).

6.1 QUALITY MANAGEMENT AND CONTROL

6.1.1 Quality Management

- 6.1.1.1 The Sponsor should implement a quality management system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials.
- 6.1.1.2 The Sponsor should focus on trial activities that promote human participant protection and reliability of trial results. These include:
 - a) Utilization of qualified individuals, as appropriate, throughout all stages of the trial process, from designing the protocol and CRF to analysing and preparing the clinical trial reports.
 - b) Designating appropriately qualified medical personnel to be available to advise on trial-related medical questions and problems.
 - c) Ensuring that all aspects of the trial are operationally feasible and avoiding unnecessary complexity, procedures and data collection.
- 6.1.1.3 A number of different quality management systems may be used and should be proportionate to the risks inherent in the trial. Regardless of

the system used, a risk-based approach should be adopted which focuses on:

- a) Identification of processes and data that are critical to assure human participant protection and reliability of trial results. This should occur during the development of the protocol.
- b) Identification of potential risks to critical trial processes and data. Such risks should include systems (e.g. trial facilities, SOPs, computerized systems, vendors) and clinical trial processes (e.g. trial design, data collection and recording, IP).
- c) Risk evaluation, including the likelihood of errors occurring given existing risk controls, the potential impact of such error on human participant protection and reliability of trial results, and the extent to which such errors would be detectable.
- d) Risk control: Sponsors should incorporate risk mitigation activities in the protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to protocols and SOPs, and adequate training in processes and procedures.
- e) Risk communication to stakeholders to facilitate risk review and continual improvement during the conduct of the clinical trial.
- f) Periodical risk review to ascertain whether the quality management activities remain effective and relevant.
- g) Risk reporting by means of clinical study reports.

6.1.2 Quality Assurance and Quality Control

6.1.2.1 The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written 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).

6.1.2.2 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.

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

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

6.2 RESPONSIBILITIES OF THE SPONSOR

6.2.1 Trial design:

6.2.1.1 The Sponsor should utilise qualified individuals (e.g. biostatisticians, clinical pharmacologists, physicians, etc) 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.

- 6.2.1.2 If the trial is a multicentre and/or multi-country trial, any differences in trial designs between the South African and other sites, must be clearly documented and explained in the trial protocol and/or related documents.
- 6.2.2 Investigator selection:
 - 6.2.2.1 Sponsors should only select investigator(s) who are:
 - a) Qualified by training and experience, and
 - b) Have adequate resources to conduct the proposed clinical trial.
 - 6.2.2.2 Before entering an agreement with an investigator to conduct a trial, the Sponsor should provide the Investigator with the clinical trial protocol and up-to-date IB, and should provide sufficient time for the Investigator to review these documents.
 - 6.2.2.3 The Sponsor should obtain the Investigator's agreement:
 - a) To conduct the trial in compliance with these Guidelines, ICH GCP, the requirements of the South African regulatory authority and with the protocol agreed to by the Sponsor and given approval by the relevant REC;
 - b) To comply with procedures for data recording and 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.
 - 6.2.2.4 The Sponsor and the Investigator must sign the protocol, or an alternative document, to confirm this agreement.
- 6.2.3 Submission to SAHPRA: Before initiating a clinical trial in South Africa, the Sponsor and the Investigator must obtain approval from SAHPRA to begin the trial.
- 6.2.4 Confirmation of review and approval by REC
 - 6.2.4.1 The Sponsor should obtain from the PI:
 - a) the name and address of the relevant REC registered with NHREC, and
 - b) documented REC approval.
 - 6.2.4.2 If the REC grants approval conditional on required modifications, the Sponsor should obtain a copy of the modification(s) made and the date the final approval was granted by the REC.
 - 6.2.4.3 The Sponsor should obtain from the PI documentation and dates of any REC re-approvals/re-evaluations, and of any withdrawals or suspensions of approval.
- 6.2.5 South African National Clinical Trials Register (SANCTR)
 - 6.2.5.1 All clinical trials to be conducted in South Africa must register with the SANCTR. Registration with the SANCTR requires that a trial is

approved by a REC and meets the requirements of SAHPRA. SANCTR facilitates registration of trials in accordance with the WHO's International Clinical Trials Registry Platform initiative that requires prior entry of clinical trials in a public registry as a condition for publication.

- 6.2.5.2 The Sponsor must ensure that a trial is fully registered on the SANCTR before participants are enrolled. The Investigator and the Sponsor must communicate the information required to register the trial. For Investigator-initiated trials, the Investigator must register the trial.
- 6.2.5.3 Clinical trials are registered at <http://www.sanctr.gov.za>.
- 6.2.6 The Sponsor should provide insurance for all trial participants. In addition, they should indemnify (legal and financial coverage) the Investigator/Institution against claims arising from the trial, except for claims that arise from professional malpractice and/or negligence.
- 6.2.7 The financial aspects of the trial should be documented in a CTA between the Sponsor and the Investigator/Institution. A signed declaration must be provided by the Sponsor which states that there are sufficient funds available to complete the trial.
- 6.2.8 Prior to initiating a trial, the Sponsor should define, establish and allocate all trial-related duties and functions.

6.3 CONTRACT RESEARCH ORGANIZATION (CRO)

- 6.3.1 A Sponsor may transfer any or all of the Sponsor's trial-related duties and functions to a CRO, but ultimate responsibility for quality and integrity of trial data always remains with the Sponsor. Although the CRO must implement quality assurance and quality control, the Sponsor is responsible specifically for:
 - 6.3.1.1 Ensuring oversight of any trial-related duties and functions carried out on its behalf; and
 - 6.3.1.2 Ensuring that the relevant CRO has the required skills, experience and competencies to conduct clinical trials.
- 6.3.2 Any trial-related duty and function that is transferred to and assumed by a CRO must be specified in writing. In addition, the Sponsor must approve in writing any further sub-contracting of trial-related duties and functions by the CRO.
- 6.3.3 Any trial-related duty and function not specifically transferred to and assumed by a CRO remains with the Sponsor.

NOTE: All references to Sponsor in this guideline apply to a CRO to the extent that the CRO has assumed the trial-related duties and functions of the Sponsor.

6.4 TRIAL MANAGEMENT, DATA HANDLING AND RECORD KEEPING

- 6.4.1 The Sponsor must use appropriately qualified individuals to supervise overall conduct of the trial, to handle and verify data, to conduct statistical analyses, and to prepare the trial reports.
- 6.4.2 The Sponsor may establish an independent Data Safety Monitoring Board (DSMB) to assess progress of a clinical trial, including safety data and critical efficacy endpoints at intervals, and to recommend to the Sponsor whether to continue, modify or stop a trial. The DSMB must have written SOPs and must maintain written records of all its meetings.
- 6.4.3 When using electronic trial data handling and/or remote electronic trial data systems, the Sponsor must:
 - 6.4.3.1 Ensure and document that the systems conform to established requirements for completeness, accuracy, reliability and consistent intended performance (i.e. validation).
 - 6.4.3.2 The Sponsor must base its approach to validation of systems on a risk assessment that considers the intended use of the system and its potential to affect human participant protection and the reliability of trial results.
 - 6.4.3.3 Maintain SOPs for using these systems. Such SOPs should:
 - a) Cover system setup, installation and use;
 - b) Describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning and re-commissioning;
 - c) Describe the responsibilities of the Sponsor, Investigator and other parties with respect to the use of these computerised systems; and
 - d) Make provision for training by all users.
 - 6.4.3.4 Ensure that the systems are designed to document data changes without deleting previously entered data (i.e. maintain an audit trail).
 - 6.4.3.5 Maintain a security system that prevents unauthorized access to the data.
 - 6.4.3.6 Maintain a register of persons authorized to make data changes.
 - 6.4.3.7 Maintain adequate data backup.
 - 6.4.3.8 Ensure that blinding, if any, is maintained during data entry and processing.
 - 6.4.3.9 Ensure the integrity and confidentiality of data, including any that describe the context, content and structure of the data – especially when making changes to computerized systems.
- 6.4.4 If data are transformed during processing, it must be possible to compare the original data and observations with the processed data.
- 6.4.5 The Sponsor must use an unambiguous participant identification code that allows identification of all data reported for each participant.

- 6.4.6 The Sponsor, or other owners of the data, must retain all the Sponsor-specific essential documents pertaining to the trial for not less than 10 years or until at least two years have elapsed since the formal discontinuation of clinical development of the IP.
- 6.4.7 If the Sponsor discontinues clinical development of an IP, the Sponsor must notify all Investigators and SAHPRA.
- 6.4.8 The Sponsor must inform the Investigator in writing of the need for record retention and must notify the Investigator in writing when the trial-related records are no longer needed.
- 6.4.9 Any transfer of ownership of the data must be reported to SAHPRA.

6.5 INFORMATION ON INVESTIGATIONAL PRODUCTS

- 6.5.1 When planning trials, a Sponsor should ensure that sufficient safety and efficacy data from pre-clinical studies and/or clinical trials are available to support human exposure using the proposed route, dosages, duration and in the trial population to be studied.
- 6.5.2 The Sponsor must update the IB as new information becomes available.

6.6 MANUFACTURING, PACKAGING, LABELLING, AND CODING INVESTIGATIONAL PRODUCTS

- 6.6.1 The Sponsor must ensure that the IP (including active comparator and placebo, if applicable) is characterised as appropriate for the stage of development of the product, is manufactured in accordance with any applicable GMP standards, and is coded and labelled in a manner that protects blinding, if applicable. Labelling must comply with South African regulatory requirements, including the Medicines and Related Substances Act No. 101 of 1965, and Regulation 30(9) (R.859 in GG 01464 dated 25 August 2017).
- 6.6.2 The Sponsor must determine the 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 GPP standards is required, where applicable. The Sponsor must inform all parties involved (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.
- 6.6.3 The IP must be packaged to prevent contamination and deterioration during transport and storage.
- 6.6.4 In blinded trials, the coding system for the IP must include a mechanism that permits rapid identification of the IP in case of a medical emergency but does not permit undetectable breaks of blinding.
- 6.6.5 If significant formulation changes are made to the IP or comparator product during the course of clinical development, the results of any additional studies of the formulated product (e.g. stability, dissolution rate, bioavailability)

necessary to assess whether the pharmacokinetic profile of the product is significantly altered must be available before use of the new formulation in clinical trials.

6.7 SUPPLYING, HANDLING INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED WASTE

- 6.7.1 The Sponsor is responsible for supplying a sufficient quantity of IP.
- 6.7.2 The Sponsor must not supply an Investigator with IP until the Sponsor obtains all required documentation (e.g. REC and SAHPRA approval and other regulatory documentation).
- 6.7.3 The Sponsor must ensure that written procedures include instructions and relevant documents for the Investigator to follow for handling and storage of IP for the trial. The procedures must address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from participants, and return of unused IP to the Sponsor (or alternative disposition if authorised by the Sponsor and in compliance with the SAHPRA-approved protocol).
- 6.7.4 The Sponsor must:
 - 6.7.4.1 Ensure timely delivery of IP to the Investigator.
 - 6.7.4.2 Maintain records that document shipment, receipt, disposition, return and destruction of the IP.
 - 6.7.4.3 Maintain a system for retrieving IP and documenting such retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).
 - 6.7.4.4 Maintain a system for disposal of unused IP and for its documentation. Disposal must be done according to South African regulations.
 - 6.7.4.5 Take steps to ensure that IP is stable over the period of use.
 - 6.7.4.6 Maintain sufficient quantities of IP used in the trials to reconfirm specifications, if necessary, and maintain records of batch sample analyses and characteristics. To the extent that IP stability permits, samples should be retained until analyses of trial data are complete or as required by the applicable regulatory requirement(s), whichever is longer.
 - 6.7.4.7 The sponsor must provide and maintain a system for retrieving and disposal of trial-related waste (e.g. syringes and needles).

6.8 RECORD ACCESS

- 6.8.1 The Sponsor must ensure that the protocol or other written agreement specifies that the Investigator must provide direct access to source data/documents for trial-related monitoring, audits, REC review and regulatory inspection.

- 6.8.2 The Sponsor must verify that each participant has consented to direct access to his/her original medical records for trial-related monitoring, audit, REC review and regulatory inspection.

6.9 SAFETY INFORMATION

- 6.9.1 The Sponsor is responsible for ongoing safety evaluation of IP.
- 6.9.2 The Sponsor must promptly provide written notification to the Investigator and SAHPRA of findings that may adversely affect the safety of participants, affect the conduct of the trial and/or change the REC's approval to continue the trial.
- 6.9.3 The commitment to provide safety information must be included in the CTA signed between the Sponsor and the Investigator.

6.10 ADVERSE DRUG REACTION REPORTING

- 6.10.1 The Sponsor must expedite reporting of all adverse drug reactions (ADRs) that are both serious and unexpected to all concerned, including the Investigator and SAHPRA.
- 6.10.2 Expedited reporting should occur within the timeframe and format specified by SAHPRA.
- 6.10.3 The Sponsor must submit all safety updates and periodic reports to SAHPRA as required.

6.11 MONITORING

- 6.11.1 The purpose of trial monitoring is to verify that:
- 6.11.1.1 The rights and well-being of human participants are protected;
 - 6.11.1.2 Reported trial data are accurate, complete and verifiable from source documents;
 - 6.11.1.3 The trial is conducted in compliance with the currently approved protocol (including any amendments), with SA GCP 2020 and with SAHPRA requirements.
- 6.11.2 Selection and Qualifications of Monitors
- Monitors should be
- 6.11.2.1 Appointed by the Sponsor.
 - 6.11.2.2 Appropriately trained, with the scientific and/or clinical knowledge necessary to monitor the trial adequately. A monitor's qualifications should be documented.
 - 6.11.2.3 Thoroughly familiar with the IP, the protocol, the informed consent documents and other written information to be provided to participants, the Sponsor's SOPs, SA GCP 2020, and SAHPRA requirements.
- 6.11.3 Extent and Nature of Monitoring:
- 6.11.3.1 The Sponsor must ensure that trials are adequately monitored in accordance with SAHPRA requirements. The Sponsor should determine the appropriate extent and nature of monitoring based on

considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial.

- a) In general, on-site monitoring is necessary before, during and after the trial;
- b) Statistically controlled sampling may be acceptable for selecting data to be verified.

6.11.3.2 The Sponsor must develop a systematic, prioritized, risk-based approach to monitoring clinical trials. Flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. A combination of on-site and centralized monitoring activities may be appropriate. The sponsor should document the rationale for the chosen monitoring strategy (e.g. in the monitoring plan).

6.11.3.3 On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner.

6.11.3.4 Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring by such methods as:

- a) Routine review of submitted data;
- b) Identification of missing data, inconsistent data, data outliers or unexpected lack of variability and protocol deviations that may be indicative of systematic or significant errors in data collection and reporting at a site or across sites, or may be indicative of potential data manipulation or data integrity problems;
- c) Using statistical analyses to identify data trends such as the range and consistency of data within and across sites;
- d) Analysing site characteristics and performance metrics;
- e) Selection of sites and/or processes for targeted on-site monitoring.

6.11.4 Monitor's Responsibilities:

In accordance with the Sponsor's requirements, the Monitor must ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

6.11.4.1 Act as the main line of communication between the Sponsor and the Investigator;

6.11.4.2 Verify that the Investigator has adequate qualifications and adequate resources throughout the trial period, and that facilities (including laboratories, equipment and staff) are adequate to safely and properly conduct the trial and remain adequate throughout the trial period;

6.11.4.3 Verify, regarding the IP:

- a) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
 - b) That IP is supplied only to trial participants who are eligible to receive it and at the protocol specified doses.
 - c) That participants are provided with the necessary instructions on properly using, handling, storing and returning IP.
 - d) That receipt, use and return of IP at the trial sites are controlled and documented adequately.
 - e) That disposal of unused IP at the trial sites complies with applicable regulatory requirements.
- 6.11.4.4 Verify that the Investigator follows the approved protocol and all approved amendments, if any.
- 6.11.4.5 Verify that written informed consent was obtained before each trial participant's participation in the trial.
- 6.11.4.6 Ensure that the Investigator receives the current IB, all documents and all trial supplies needed to conduct the trial safely and properly in compliance with SAHPRA requirements.
- 6.11.4.7 Ensure that the Investigator and the Investigator's staff are adequately informed about the trial.
- 6.11.4.8 Verify that the Investigator and the Investigator's staff are performing specified trial functions in accordance with the protocol and any other written agreement between the Sponsor and the Investigator, and that functions have not been delegated to unauthorized individuals.
- 6.11.4.9 Verify that the Investigator enrolls only eligible participants.
- 6.11.4.10 Report the participant recruitment rate.
- 6.11.4.11 Verify that source documents and other trial records are accurate, complete, kept up-to-date and maintained.
- 6.11.4.12 Verify that the Investigator provides all required reports, notifications, applications and submissions, and that these documents are accurate, complete, timely, legible, dated and identify the trial.
- 6.11.4.13 Check the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The Monitor should specifically verify that:
- a) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents;
 - b) Any dose and/or therapy modifications are well documented for each of the trial participants;
 - c) AEs, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs;
 - d) Visits that the participants fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs;

- e) All withdrawals and dropouts of enrolled participants from the trial are reported and explained on the CRFs.
 - 6.11.4.14 Inform the Investigator of any CRF entry error, omission or illegibility. The Monitor must ensure that appropriate corrections, additions or deletions are made, dated, explained (if necessary) and initialled by the Investigator or by an authorised member;
 - 6.11.4.15 Determine whether adverse events (AEs) are appropriately reported within time periods required by GCP, the protocol, the REC, the sponsor and SAHPRA;
 - 6.11.4.16 Determine whether the Investigator maintains the essential documents;
 - 6.11.4.17 Communicate deviations from the protocol, SOPs, GCP and SAHPRA requirements to the investigator and take appropriate action designed to prevent recurrence of the detected deviations.
- 6.11.5 The Monitor must follow the Sponsor's written SOPs as well as those procedures specified by the Sponsor for monitoring a specific trial.
- 6.11.6 Monitoring Report:
- 6.11.6.1 The Monitor must submit a written report to the Sponsor and the Investigator after each site visit or trial-related communication;
 - 6.11.6.2 Reports must include the date, site, name of the Monitor and name of the Investigator or other individual(s) contacted;
 - 6.11.6.3 Reports must include a summary of what the Monitor reviewed and the Monitor's statements concerning significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance;
 - 6.11.6.4 Review and follow-up of the Monitoring Report with the Sponsor must be documented by the Sponsor's designated representative;
 - 6.11.6.5 Monitoring results must be provided to the Sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up as indicated. Results of monitoring activities must be documented in sufficient detail to allow verification of compliance with the monitoring plan.
- 6.11.7 Monitoring Plan:
- 6.11.7.1 The Sponsor must develop a monitoring plan tailored to specific human participant protection and data integrity risks of the trial.
 - 6.11.7.2 The plan must:
 - a) Describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used and the rationale for their use;
 - b) Emphasize the monitoring of critical data and processes, and give particular attention to those aspects that are not routine clinical practice and that require additional training; and
 - c) Reference the applicable policies and procedures.

6.12 AUDITS

- 6.12.1 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 and the applicable regulatory requirements. The Sponsor must perform audits as part of implementing quality assurance.
- 6.12.2 Selection and Qualification of Auditors:
- 6.12.2.1 The Sponsor must appoint individuals who are independent of the clinical trials to conduct the audits.
 - 6.12.2.2 The Sponsor must ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.
- 6.12.3 Auditing Procedures:
- 6.12.3.1 The Sponsor must ensure that the audit is conducted in accordance with the Sponsor's written procedures.
 - 6.12.3.2 The Sponsor's audit plan and procedures for a trial audit must be guided by 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).
 - 6.12.3.3 Observations and findings of the auditors must be documented.
 - 6.12.3.4 To preserve independence and value of the audit function, the regulatory authority should not routinely request audit reports. A regulatory authority may request an audit report on a case by case basis when evidence of serious GCP non-compliance exists and/or during legal proceedings.
 - 6.12.3.5 When required by applicable law or regulation, the Sponsor must provide an audit certificate.

6.13 PROCEDURES TO MANAGE NON-COMPLIANCE

- 6.13.1 The Sponsor is ethically obliged to inform the appropriate REC and SAHPRA 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.
- 6.13.2 When significant non-compliance is discovered, the Sponsor must perform a root cause analysis and implement appropriate corrective and preventive actions.

6.14 PREMATURE TERMINATION OR SUSPENSION OF A TRIAL

If a trial is prematurely terminated or suspended, the Sponsor must inform the Investigator/Institution, REC and SAHPRA promptly of the termination or suspension and the reason therefore.

6.15 REPORTING AND RELEASE OF TRIAL RESULTS

- 6.15.1 The Sponsor must ensure that trial results and outcomes are reported to the Investigators and SAHPRA as well as to the Department of Health via the SANCTR.
- 6.15.2 The Sponsor and the PI are responsible for appropriate dissemination of the trial findings.
- 6.15.3 Results should be disclosed within one year of completion of analysis of the trial results.

6.16 PUBLICATION OF TRIAL RESULTS

- 6.16.1 In principle, the Investigator has a duty and a right to publish trial results, and must negotiate accordingly with the Sponsor.
- 6.16.2 For collaborative studies and multi-centre trials, publication conditions must be clearly described in the protocol, and approved by the relevant regulatory authorities.

7. CLINICAL TRIAL PROTOCOL

The contents of a trial protocol should generally include the topics mentioned below. Site specific information may be provided on separate protocol pages or addressed in a separate agreement. Some information may be in other protocol referenced documents.

7.1 GENERAL INFORMATION

- 7.1.1 Protocol title, protocol identifying number and date. Any amendments should also bear the amendment numbers and dates.
- 7.1.2 Name and address of the Sponsor and Monitor (if different from the Sponsor).
- 7.1.3 Name of the person authorised to sign the protocol and amendments on behalf of the Sponsor.
- 7.1.4 Name, address, and telephone number of the Sponsor's medical expert (or dentist when appropriate) for the trial.
- 7.1.5 Name of the Investigator responsible for conducting the trial, and the address and telephone number for the trial site.
- 7.1.6 Name, address and telephone number of the Investigator responsible for trial-related medical or dental decisions.
- 7.1.7 Name and address of the clinical laboratory and other medical or technical department or institution involved in the trial.

7.2 PROTOCOL BACKGROUND INFORMATION

- 7.2.1 Name and description of the IP.
- 7.2.2 A summary of findings from pre-clinical studies and clinical trials that potentially have clinical significance relevant to the trial.
- 7.2.3 Summary of known and potential risks of harm and likelihood of benefits, if any, to human participants.
- 7.2.4 Description of and justification for the route of administration, dosage, dosage regimen and treatment period.
- 7.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.
- 7.2.6 Description of the population to be studied.
- 7.2.7 References to literature and data relevant to the trial that provide context to the trial.

7.3 STUDY RATIONALE AND MOTIVATION

- 7.3.1 The rationale and motivation for an ethically and scientifically valid trial are to ask relevant and important questions that have significance for local and international populations. Research should be conducted in a wide range of

settings with different social, economic and geographical circumstances. Careful evaluation and examination as to current and future relevance for the research populations are required.

- 7.3.2 The rationale should demonstrate that the research question under consideration has not been substantively answered previously and that adequate systematic review of the topic under investigation has occurred. Where appropriate, the existence of equipoise must be demonstrated.
- 7.3.3 The research proposal should include descriptions of the anticipated method through which findings may be translated into mechanisms to improve the health status of South Africans.
- 7.3.4 The social context of the proposed research population and the measures to protect against unfair exploitation or increasing the vulnerability of potential participants must be described.

7.4 TRIAL OBJECTIVES AND PURPOSE

A detailed description of the objectives and the purpose of the trial must be provided.

7.5 TRIAL DESIGN

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

- 7.5.1 A clear statement of the primary and secondary endpoints, if any, to be measured during the trial.
- 7.5.2 The type of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of the design, procedures and stages.
- 7.5.3 The measures to minimise or avoid bias, including:
 - 7.5.3.1 Randomisation and blinding
 - a) Clinical equipoise is the principled basis for randomisation of participants: a genuine uncertainty exists about the IP or intervention that underpins the justification for the trial.
 - b) Randomisation or a propensity score prevents bias in allocation of participants into different trial arms (e.g. treatment and control arms) and thus assists to obtain an outcome that reduces the uncertainty expressed by the concept.
- 7.5.4 Use of placebo
 - 7.5.4.1 If use of a placebo is proposed, this must be properly justified in terms of the Declaration of Helsinki and contextualised for local circumstances.
 - 7.5.4.2 In principle, use of placebo in clinical trials is morally justifiable only when it is scientifically justifiable, i.e. a placebo may be used when there is no evidence that an existing treatment is more effective than placebo would be or where no proven treatment exists and

use of the placebo will not pose a risk of serious or irreversible harm to participants.

- 7.5.4.3 Placebo may be used as a comparator when no established effective intervention for the condition under study exists, or when placebo is added to an established effective intervention.
- 7.5.4.4 When an established effective intervention exists, placebo may be used as a comparator without the established effective intervention only if:
 - a) Compelling scientific reasons indicate use of placebo; and
 - b) Delaying or withholding the established effective intervention poses no more than a minor increase over minimal risk of harm to the participant; and
 - c) The risk is minimised, including through the use of effective mitigation procedures.
- 7.5.5 The trial treatment, dosage and dosage regimen of the IP, as well as the dosage form, packaging and labelling of the IP.
- 7.5.6 The expected duration of participation, the sequence and duration of trial periods, including follow-up, if any.
- 7.5.7 The "stopping rules" or "discontinuation criteria" for individual participants, for parts of trial and for the whole trial.
- 7.5.8 Accountability procedures for the IP, including placebo and comparator, if any.
- 7.5.9 Maintenance of trial treatment randomisation codes and procedures for breaking codes.
- 7.5.10 Identification of any data to be recorded directly on CRFs (i.e. without prior written or electronic record of data), to be considered to be source data.

7.6 SELECTION OF TRIAL PARTICIPANTS AND WITHDRAWAL FROM TRIAL INTERVENTION

The following must be included:

- 7.6.1 Participant inclusion criteria.
- 7.6.2 Participant exclusion criteria.
- 7.6.3 Participant withdrawal criteria (i.e. to terminate trial intervention) and procedures that specify:
 - 7.6.3.1 When and how to withdraw participants from the IP treatment;
 - 7.6.3.2 The type and timing of data to be collected for withdrawn participants;
 - 7.6.3.3 Whether and how participants are to be replaced;
 - 7.6.3.4 Follow-up for participants withdrawn from IP intervention/trial participation.

NOTE: Withdrawal from trial intervention does not necessarily mean withdrawal from trial participation

7.7 INVESTIGATIONAL PRODUCT, COMPARATOR AND CONCOMITANT MEDICATION

- 7.7.1 The IP and comparator medication, if applicable, to be administered, including the name of the product, the dose, the dosing schedule, the route of administration and the administration period.
- 7.7.2 Concomitant medication permitted (including rescue medication) or not permitted before and/or during the trial.
- 7.7.3 Procedures for monitoring participant compliance.

7.8 ASSESSMENT OF EFFICACY

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

7.9 ASSESSMENT OF SAFETY

- 7.9.1 Specification of safety parameters.
- 7.9.2 The methods and timing for assessing, recording and analysing safety parameters.
- 7.9.3 Procedures for eliciting reports of and for recording and reporting AEs and intercurrent illnesses.
- 7.9.4 The type and duration of the follow-up of participants after AEs.
- 7.9.5 The protocol must make provision for appropriate therapy to manage any AEs.

7.10 STATISTICS

- 7.10.1 Describe the statistical methods to be used, including the timing of planned interim analyses, if applicable.
- 7.10.2 State the number of participants to be enrolled. In multi-centre trials, the number of participants projected for each trial site must be specified. Provide the reason for the choice of sample size, including discussion and calculations of the power of the trial and the clinical justification.
- 7.10.3 Justify the significance level to be used.
- 7.10.4 Describe the criteria for termination of the trial.
- 7.10.5 Describe the procedure for accounting for missing, unused and spurious data.
- 7.10.6 Describe the procedures to describe and report deviation from the original statistical plan.
- 7.10.7 Describe the selection of participants to be included in the analyses (e.g. all randomized participants, all dosed participants, all eligible participants, all evaluable participants).

7.11 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

- 7.11.1 The Sponsor must ensure that the protocol and/or other written agreement specifies that the Investigator must provide direct access to source data and documents for trial-related monitoring, audits, REC review and regulatory inspection.
- 7.11.2 The Sponsor must verify that each participant has consented to direct access to his/her original medical records for trial-related monitoring, audit, REC review and regulatory inspection.

7.12 ETHICAL CONSIDERATIONS

- 7.12.1 Before submission of the protocol to the REC and SAHPRA, the local PI must describe ethical considerations pertaining to local conditions relating to the trial (see 3.1 and 3.2 of DoH 2015), including how the following aspects are addressed:
- 7.12.1.1 Multi-centre or multi-national and collaborating trials with international research groups must comply with all local i.e. South African regulatory requirements;
 - 7.12.1.2 The trial design must be customised appropriately for the local setting to ensure that local realities are considered and appropriately integrated into the design.
- 7.12.3 SAHPRA and RECs must review proposals carefully to ensure that feasible and appropriate modifications are made for the local context.
- 7.12.4 In the interests of capacity building and transformation, SAHPRA and RECs should note, for multi-national trials, whether a reasonable proportion of significant project team members including scientists and health care professionals, are South African researchers, including those from previously disadvantaged backgrounds.
- 7.12.5 If South Africa is selected as a clinical trial site but the country of origin or other high income countries are not, the Sponsor must explain the reason thereof and provide a clear ethical justification.

7.13 DATA HANDLING AND RECORD KEEPING

The aim of data management is to turn the information collected from a participant, efficiently and without errors, into data in the statistical database. All steps involved in this process must be documented to allow for step-by-step retrospective assessment of data quality and study performance, i.e. an audit trail.

7.14 FINANCING AND INSURANCE

Describe arrangements for financing and insurance (trial and malpractice), if not addressed in a separate agreement.

7.15 PUBLICATION POLICY

Describe the publication policy, if not addressed in a separate agreement.

7.16 SUPPLEMENTS TO THE PROTOCOL

Since the protocol and the clinical trial report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.

8 INVESTIGATOR'S BROCHURE

8.1 INTRODUCTION

- 8.1.1 The IB is a compilation of clinical and pre-clinical data on the IP relevant to study of the product in human participants. Its purpose is to provide Investigators and others involved in the trial with information to facilitate understanding of the rationale for, and compliance with, key features of the protocol, such as dose, dose frequency and interval, methods of administration and safety monitoring procedures.
- 8.1.2 The IB supports clinical management of participants during the clinical trial. The information must be presented in a concise, simple, objective, balanced and non-promotional form to enable a clinician or potential Investigator to understand and make an unbiased risk-benefit assessment of the appropriateness of the proposed trial. Accordingly, a medically qualified person should participate in editing the IB, subject to approval by the disciplines that generated the described data.
- 8.1.3 The type and extent of information available will vary according to the stage of development of the IP. If the IP is marketed and its pharmacology widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet or labelling may be an appropriate alternative, provided it includes current, comprehensive and detailed information on aspects of the IP of importance to the Investigator. If a marketed product is studied for a new use (i.e. a new indication), an IB specific to the new use must be prepared.
- 8.1.4 The IB should be reviewed at least annually and revised as necessary in compliance with the Sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and generation of relevant new information. However, in accordance with GCP, important new information must be communicated to Investigators, and preferably to the REC and SAHPRA before it is included in a revised IB.
- 8.1.5 Generally, the Sponsor must ensure that an up-to-date IB is available to the Investigator; Investigators must provide it to the responsible REC.
- 8.1.6 In the case of an Investigator-Sponsored trial, the Sponsor-Investigator must determine whether an IB is available from the commercial manufacturer. If the IP is provided by the Sponsor-Investigator, then he/she must provide the necessary information to the trial personnel.
- 8.1.7 Where preparation of a formal IB is impractical, the Sponsor-Investigator must substitute an expanded background information section in the protocol that describes the minimum current information as described in this guideline.

8.2 CONTENT OF INVESTIGATOR'S BROCHURE

The IB should contain the following sections, each with literature references where appropriate:

- 8.2.1 Table of Contents.
- 8.2.2 Summary: A brief summary (preferably not exceeding two pages) must highlight the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information available that is relevant to the stage of clinical development of the IP.
- 8.2.3 A brief introductory statement should contain the chemical name (and generic and trade name for an approved product) of the IP, all active ingredients in the IP, its pharmacological class and expected position within this class (e.g. advantages), the rationale for conducting research with the IP, and the anticipated prophylactic, therapeutic and/or diagnostic indications. Describe the general approach to be followed in evaluating the IP.
- 8.2.4 Physical, Chemical, and Pharmaceutical Properties and Formulation.
- 8.2.5 Pre-clinical Studies: The results of relevant pre-clinical pharmacology, toxicology, pharmacokinetic and IP metabolism studies must be provided in summary form which should address the methodology used, the results and a discussion of the relevance of the findings to the investigated therapeutic (and possible unfavourable or unintended) effects in humans.
- 8.2.6 Effects in Humans: Discuss the known effects of the IP in humans, including pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities. Where possible, provide a summary of each completed clinical trial. Provide information about results of any use of the IP other than in clinical trials, such as experience during marketing.
- 8.2.7 Summary of Data and Guidance for the Investigator: This section must provide an overall discussion of pre-clinical and clinical data, to synthesise the information from various sources on different aspects of the IP(s), wherever possible. In this way, an Investigator has the most informative interpretation of available data with an assessment of implications of the information for future clinical trials. Where appropriate, published reports on related products should be discussed to help the Investigator to anticipate ADR or other problems in clinical trials.

9 ESSENTIAL DOCUMENTS TO CONDUCT A CLINICAL TRIAL

9.1 INTRODUCTION

- 9.1.1 Essential Documents individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents demonstrate compliance by the Investigator, Sponsor and Monitor with the standards of GCP and applicable regulatory requirements.
- 9.1.2 Filing Essential Documents at Investigator and Sponsor sites in a timely manner assists with management of a trial by the Investigator, Sponsor and Monitor.
- 9.1.3 These documents are usually audited during the Sponsor's independent audit function and inspected by SAHPRA to confirm validity of the trial conduct and integrity of data collected.
- 9.1.4 The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated:
- 9.1.4.1 Before the clinical phase of the trial commences;
 - 9.1.4.2 During the clinical conduct of the trial; and
 - 9.1.4.3 After completion or termination of the trial.
- The purpose of each document, and whether it should be filed in either the Investigator/Institution or Sponsor files, or both is described. Documents may be combined, provided the individual elements are readily identifiable.
- 9.1.5 Trial Master Files (TMF) must be established at the beginning of the trial, at both the Investigator's site and at the Sponsor's office. A final close-out of a trial can be done only when both Investigator and Sponsor TMFs have been reviewed, reconciled and confirmed that all necessary documents are in the appropriate files.
- 9.1.6 Any of the documents addressed in this guideline must be available for audit by the Sponsor's auditor and inspection by SAHPRA.

9.2 BEFORE THE CLINICAL PHASE OF THE TRIAL COMMENCES

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

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the Investigator	X	X
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	X
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	To document that recruitment measures are appropriate and not coercive	X	
FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the Investigator/Institution and the Sponsor for the trial	X	X
INSURANCE STATEMENT (where required)	To document that compensation to participant(s) for trial-related injury will be available	X	X
SIGNED AGREEMENT BETWEEN INVOLVED PARTIES e.g.	To document agreements		
- Investigation/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
DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF REC OF THE FOLLOWING:	To document that the trial has been participant to REC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X
- 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;			
- Any other documents given approval/favourable opinion			

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
REC COMPOSITION	To document that the REC is constituted in accordance with GCP	X	X (where required)
REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL (where required)	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)
CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUBINVESTIGATOR(S)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of participants	X	X
NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and/or ranges of the tests	X	X
MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/ TESTS - Certification; - Accreditation; - Established quality control and/or external quality assessment; or - Other validation	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the participants		X
INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or IB)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS	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
CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S)	To document identity, purity and strength of investigational product(s) to be used in the trial		X
DECODING PROCEDURES FOR BLINDED TRIALS	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)
MASTER RANDOMISATION LIST	To document method for randomisation of trial population		X (third party if applicable)
PRE-TRIAL MONITORING REPORT	To document that the site is suitable for the trial (may be combined with the trial initiation monitoring report)		X

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
TRIAL INITIATION MONITORING REPORT	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

9.3 DURING THE CLINICAL CONDUCT OF THE TRIAL

The following must be added to the files during the trial to evidence that all new relevant information is documented as it becomes available.

Title of Document	Purpose	Located in Files of	
		Investigator / Institution	Sponsor
INVESTIGATOR'S BROCHURE UPDATES	To document that Investigator is informed in a timely manner of relevant information as it becomes available	X	X
ANY REVISION TO: – 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
DATED, DOCUMENTED APPROVAL/ FAVOURABLE OPINION OF REC OF THE FOLLOWING: – Protocol amendment(s) – Revision(s) of informed consent form and/or 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 REC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X
REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/ NOTIFICATIONS WHERE REQUIRED FOR: – Protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUBINVESTIGATOR(S)		X	X
UPDATES TO NORMAL VALUE(S)/ RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and ranges that are revised during the trial	X	
UPDATES OF MEDICAL/ LABORATORY/TECHNICAL PROCEDURES/TESTS <ul style="list-style-type: none"> - 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	X (where required)	X
DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT	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
CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS	To document identity, purity and strength of investigational product(s) to be used in the trial		X
MONITORING VISIT REPORTS	To document site visits by, and findings of, the monitor		X
RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS <ul style="list-style-type: none"> - Letters - Meeting notes - Notes of telephone calls 	To document any agreements or significant discussions regarding trial administration, protocol deviations/ violations, trial conduct, adverse event (AE) reporting	X	X
SIGNED INFORMED CONSENT FORMS	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	X	
SOURCE DOCUMENTS	To document the existence of the participant and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of participant	X	
SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
DOCUMENTATION OF CRF CORRECTIONS	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS	Notification by originating investigator to Sponsor of serious adverse events and related reports in accordance with the South African Good Clinical Practice: Clinical Trials Guidelines.	X	X

Title of Document	Purpose	Located in Files of	
		Investigator / Institution	Sponsor
NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND REC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION	Notification by Sponsor and/or investigator, where applicable, to regulatory authorities and REC(s) of unexpected serious ADRs in accordance with SA GCP	X (where required)	X
NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION	Notification by Sponsor to Investigators of safety information in accordance with the SA GCP.	X	X
INTERIM OR ANNUAL REPORTS TO REC AND AUTHORITIES	Interim or annual reports provided to REC and to authorities in accordance with accordance with SA GCP.	X	X (where required)
PARTICIPANT SCREENING LOG	To document identification of participants who entered pre-trial screening	X	X (where required)
PARTICIPANT IDENTIFICATION CODE LIST	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	
PARTICIPANT ENROLMENT LOG	To document chronological enrolment of participants by trial number	X	
INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE	To document that IP(s) have been used according to the protocol	X	X
SIGNATURE SHEET	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
RECORD OF RETAINED BODY FLUIDS/TISSUE SAMPLES (IF ANY)	To document location and identification of retained samples if assays need to be repeated	X	X

9.4 AFTER COMPLETION OR TERMINATION OF THE TRIAL

After completion or termination of the trial, all the documents identified in sections 9.2 and 9.3 should be in the file together with the following:

Title of Document	Purpose	Located in Files of	
		Investigator / Institution	Sponsor
INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE	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

Title of Document	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION	To document destruction of unused investigational products by Sponsor or at site	X (if destroyed at site)	X
COMPLETED PARTICIPANT IDENTIFICATION CODE LIST	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	
AUDIT CERTIFICATE (if available)	To document that audit was performed		X
FINAL TRIAL CLOSE-OUT MONITORING REPORT	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
TREATMENT ALLOCATION AND DECODING DOCUMENTATION	Returned to Sponsor to document any decoding that may have occurred		X
FINAL REPORT BY INVESTIGATOR TO REC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)	To document completion of the trial	X	
CLINICAL STUDY REPORT	To document results and interpretation of trial	X (if applicable)	X

10 OTHER RELEVANT CONSIDERATIONS

10.1 CONFLICT OF INTEREST (COI)

10.1.1 A COI arises when a secondary interest (e.g. scientific recognition or financial gain) conflicts with the ethical conduct of research, the primary goal of health-related research. A COI may, or may be perceived, to directly or indirectly influence research activities, including but not limited to the choice of research questions and methods, recruitment and retention of participants, interpretation and reporting of data.

10.1.2 COIs pose concerns because of the potential to affect the well-being of participants, as well as the integrity of the research.

10.1.3 Conflicts may arise naturally from engagement between researchers, universities, Sponsors, funders, RECs, regulatory authorities and other entities.

NOTE: The mere existence of a COI does not necessarily imply wrongdoing.

10.1.4 COIs must be identified, disclosed and properly managed or eliminated to ensure transparency and accountability in trials.

10.1.5 Institutions that host clinical trials and RECs that review proposals for clinical trials must have clearly formulated COI policies and SOPs; relevant personnel must know how to make disclosure and how to manage disclosures of affiliation with, or financial involvement in, any organization or entity with an interest in the subject matter or materials of researchers.

10.1.6 The range of potential interests includes direct benefits, such as sponsorship of the investigation, indirect benefits, such as provision of material or facilities, and support of individuals, such as provision for travel or accommodation expenses to attend conferences. Disclosure should cover any situation in which COI may, or may be perceived to, affect decisions.

10.1.7 Each individual is responsible for recognising situations in which he/she may have or may be perceived to have a COI, or might reasonably be seen by others to have a conflict, and to disclose to the appropriate person or entity and to follow the policy and procedures.

10.1.8 If an individual is uncertain about the existence of a COI, enquiries should be made to the appropriate person as per the policy.

10.2 INSURANCE AGAINST TRIAL-RELATED INJURIES

10.2.1 Basic Principles:⁵

10.2.1.1 Research participants should not bear any financial cost to rectify harms that occur as a result of trial participation. It is thus essential that provision is made for comprehensive insurance against trial-related bodily injury.

⁵ See also 3.5.3 in DoH 2015.

- 10.2.1.2 Sponsors adopt the morally right convention of paying for insurance cover for medical treatment in the event of trial-related injuries, including death. In South Africa, it is mandatory to have adequate comprehensive insurance cover for clinical trials, and RECs and regulatory authority should assess that it is in place.
 - 10.2.1.3 The insurer pays the medical costs of necessary treatment to restore the participant to his/her previous position, if possible.
 - 10.2.1.4 Payment of medical expenses by the insurer is triggered when bodily or other injury is attributable to trial participation. In the case of an *in utero* injury due to the mother's participation, payment for medical expenses proceeds as though the unborn child is a research participant.
 - 10.2.1.5 In principle, only bodily injuries of an enduring and disabling character (including exacerbation of an existing condition) and/or death are covered by the insurance. Temporary pain or discomfort or less serious or curable complaints are generally not regarded as trial-related bodily injury. In the case of bodily injury caused by the response to an AE to a medicinal product under trial, the insurance cover will apply.
 - 10.2.1.6 Payment for medical expenses is made without acknowledgement of any legal liability and is thus to be understood to be an *ex gratia* payment.
 - 10.2.1.7 The provision of insurance cover and payment of medical expenses does not mean that an injured participant may not pursue legal action against the Sponsor to claim compensation based for negligence in a South African court for loss or harm not covered by the insurance. However, an argument that pain and suffering, loss of income and other possible claims should be paid for by the Sponsor's insurer is not sound in South African law and will not succeed.⁶
- 10.2.2 The insurance cover usually does not extend to situations where:
- 10.2.2.1 An IP fails to demonstrate its intended effect or to provide any other benefit to the participant;
 - 10.2.2.2 Participants receive placebo which fails to provide a therapeutic effect; and
 - 10.2.2.3 Events occur that are not part of the trial protocol.
- 10.2.3 Insurance cover may be limited in some instances:
- 10.2.3.1 Where bodily injury arises in circumstances that involve:
 - a) a significant departure from the approved protocol;
 - b) the wrongful act or omission of a third party, including a clinician's failure to deal adequately with an AE; and/or
 - c) contributory negligence by the participant,

⁶ See 3.5.3 in DoH 2015.

the amount paid should be appropriate to the nature, severity and persistence of the bodily injury, and should be consistent with the amount of damages (compensation) that would ordinarily be awarded by a South African court for similar injuries in instances where legal liability is admitted.

10.2.3.2 The amount to be paid may be abated (diminished), or in certain circumstances excluded, in light of:

- a) the seriousness of the bodily injury being treated;
- b) the degree of probability that ADRs would occur and the warnings given to the participant; and/or
- c) the risks and benefits of established treatments relative to those known or suspected of the IP.

10.2.3.3 The interpretation and weighting of factors depend on the level of risk that a participant can reasonably be expected to accept. This approach reflects the fact that flexibility is required in relation to a particular participant's circumstances.

10.2.4 Dispute resolution regarding the amount to be paid:

10.2.4.1 In a situation where an insurer is willing to pay for medical expenses, but a difference of opinion exists between the Sponsor and the participant as to the appropriate amount of money to be paid, the recommendation is that the Sponsor should seek, as its own cost, the opinion of a mutually acceptable independent expert.

10.2.4.2 This opinion must be provided to the participant in the interest of fairness and should be given substantial weight by the Sponsor in reaching its decision on the appropriate payment to be made.

10.2.5 Lodging a claim

10.2.5.1 A participant who wishes to lodge a claim pursuant to these guidelines should deal with the Sponsor, preferably via the PI.

10.2.5.2 The claim must set out in detail the nature and background to the bodily injury. The Sponsor should be permitted to review medical records relevant to the claim whereafter the Sponsor should process the claim expeditiously.

10.2.5.3 Ordinarily, when payment is made, a participant will be asked to indicate in writing that he/she accepts payment as full settlement of the medical expenses claim. However, this undertaking does not necessarily rule out legal action on a different basis (see 10.2.1.7 above).

NOTE: Insurance against trial-related bodily injury does not replace a clinician's malpractice insurance.

10.3 PROFESSIONAL INDEMNITY

All Investigators require comprehensive current professional indemnity (malpractice) insurance to cover any claims relating to clinical negligence (i.e. activity not attributable to the research).

10.4 SPONSOR INDEMNIFICATION

The Sponsor must indemnify (provide legal and financial cover for) the Investigator against claims arising from the trial, excluding claims that arise from malpractice or negligence.

10.5 CONTINUING CARE AFTER RESEARCH (POST TRIAL ACCESS)

Refer to SAHPRA guideline titled "Post Clinical Trial Access (PTA)/Continued Access" dated June 2018 or subsequent updates for details.

10.6 ASSESSING SAFETY AND MINIMISING RISK

The informed consent document must explain clearly what to do in the event that an ADR is experienced. In the case of a pharmaceutical trial, a DSMB may be appointed, if appropriate, to oversee the trial, paying attention to safety, efficacy and interim analysis of the data. In the event of clear evidence of efficacy or none (i.e. interim results indicate that the IP works or does not work) or of harm to participants (i.e. interim results indicate unanticipated AEs) before the end of the trial, premature termination of the trial must be recommended by the DSMB on ethical and clinical grounds.

10.7 HUMAN REPRODUCTION CONSIDERATIONS

10.7.1 Pregnant women, women planning to become pregnant, or breastfeeding women are usually excluded from human clinical trials **where a new chemical entity (NCE) or medicines with no information on safety in pregnancy/lactation are investigated** for treatment of a particular disease/condition or disorder.

10.7.2 Pregnant or breastfeeding women should be included in human clinical trials where possible, i.e. when safety and other relevant information is available during a clinical trial. This is to ensure that appropriate knowledge about NCEs for this group of persons is developed.

10.7.3 When males and females of childbearing age are to be enrolled in clinical trials where medicines known to be harmful or potentially harmful to human reproduction organs and pregnancy are to be used, the appropriate international and national guidelines regulating such research, should be consulted.

10.8 NEW TECHNOLOGIES

Human biological materials and their associated data (including images) provide a rich source for research materials. An inevitable and unavoidable overlap between clinical and research domains prevails: many biological samples are collected during clinical interventions for diagnostic purposes, which means that the wish to make further use of the samples as research materials has implications for whether and how this may occur. Other samples are collected specifically for research purposes.

Use of human biological materials and their associated data facilitates research in new technologies, which include genetic and genomic research, cell and gene therapy (CGT). Somatic cell therapy is described as the administration to humans of

autologous, allogeneic or xenogeneic living non-germline cells, other than transfusable blood products, which have been manipulated or processed *ex vivo* with the goal of treating or preventing disease, supporting other therapy or diagnosis. Germline therapy is currently prohibited across the globe due to safety and ethical concerns.

Genetic information by its very nature is personal, familial and communal. Current knowledge and understanding of this information and what can be achieved through use thereof are advancing exponentially. However, current ethics and regulatory systems are criticised for not providing clear guidance to researchers on how best to be enabled to use this rich source of research material.

The fundamental ethical principles that underpin all research involving with human participants apply to proposals to use human biological materials and their associated data. Research proposals must address specifically the social value of the research especially in the local context; how consent, privacy, confidentiality will be managed; and the potential effect on families, communities and other groups. Specific concerns include protection of privacy, whether and how incidental findings are to be communicated to the person from whom the sample originates. See DoH 2015 3.3 for further discussion.

10.9 ELECTRONIC SIGNATURES

An electronic signature is a computer data compilation of any symbol or series of symbols executed, adopted or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature. In general, a signature may not be denied legal effect or validity solely because it is in electronic format, and a contract or other record relating to a transaction may not be denied legal effect, validity or enforceability solely because an electronic signature or electronic record was used in its formation. To be considered equivalent to full handwritten signatures, electronic signatures must comply with all applicable requirements under 21 CFR part 11⁷. Electronic records that are electronically signed must contain information associated with the signing that clearly indicates the printed name of the signer, the date and time when the signature was executed, and the meaning associated with the signature. In addition, electronic signatures and handwritten signatures executed to electronic records must be linked to the respective electronic records to ensure that the signatures cannot be excised, copied or otherwise transferred to falsify an electronic record by ordinary means.

10.10 THERAPEUTIC MISCONCEPTION AND DUAL ROLES

10.10.1 In a treatment context, clinicians must act in the best interests of their patients. When a patient becomes a trial participant, this obligation is more complex. Necessarily, the trial context has a different focus, i.e. the systematic generation of new knowledge within a paradigm that may or may not include direct benefit for individual participants. This implies that

⁷ FDA regulations found in part 11 set forth the criteria under which FDA considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to a handwritten signature executed on paper (see CFR 11.1(a))

the best interests of individual participants are not the focus and thus that researchers cannot simultaneously act in the best interests of the patient to change the trial protocol to suit an individual participant's interests. Instead, the best interest's criterion must be turned around: the researcher must decide whether it would be against the best interest of the patient to become or to continue as a trial participant.

- 10.10.2 The researcher must provide sufficient information so that expectations of the patient/participant are aligned appropriately to avoid potential therapeutic misconception. A therapeutic misconception prevails when a patient/participant believes that the primary purpose of a trial procedure or intervention is to confer therapeutic benefit on her rather than to generate knowledge, thus confusing the purpose of research and the purpose of treatment.
- 10.10.3 The dual role played by a clinician/researcher invites ambiguity and confusion for both patient and clinician. To prevent therapeutic misconception and even deception (intentional or unintentional) of participants, careful reflection on the duality of roles is required, and the consent process must acknowledge the difference between clinical care and clinical trial.

10.11 CONDUCTING CLINICAL TRIALS DURING A PANDEMIC

- 10.11.1 Conducting clinical trials during a pandemic results in a number of challenges, such as self-isolation, site closures, travel limitations, interruptions to the supply chain for Investigational Product (IP), and other considerations if site personnel or study participants become infected. These challenges may lead to difficulties in meeting protocol-specific procedures, including administration or use of the IP, or adhering to protocol-mandated visits and/or laboratory/diagnostic testing.
- 10.11.2 The National PI and PI, in collaboration with SAHPRA and the responsible Ethics Committee, must provide clarity to help ensure the safety of all study participants and site personnel, maintain compliance with GCP, and minimize risks to trial integrity during these times.

11 REFERENCES

CIOMS with WHO International Ethical Guidelines for Epidemiological Studies (2009)

Clinical Trial Compensation Guidelines, Association of British of Pharmaceutical Industry (ABPI) Guidelines (2014)

CFR 21 part 11, Electronic Records; Electronic Signatures - Scope and Application *Guidance for Industry*

Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research involving Human Subjects (2016)

Declaration of Helsinki (2013)

Department of Health *Ethics in Health Research: Principles, Processes and Structures* 2nd edition (2015) (referred to as DoH 2015)

ICH Harmonised Tripartite Guideline: Clinical Investigation of Medicinal Products in the Pediatric Population E11 2000

ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R2) 2016 (ICH GCP 2016)

World Health Organisation WHO Technical Report Series, No. 850 Guidelines for good clinical practice (GCP) for trials on pharmaceutical products (1995)

12 GLOSSARY

Adverse Drug Reaction (ADR)

In the preapproval 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 ADRs. 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 patient or clinical trial participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An 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 Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Amendment (to the protocol)

See Protocol Amendment.

Applicant

An individual, company, institution or organisation that acts on behalf of the Sponsor to initiate and manage the trial as its local representative.

Applicable Regulatory Requirement(s)

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

Approval (in relation to Research Ethics Committees (RECs))

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

Audit

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

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.

Audit Trail

Documentation that allows reconstruction of the course of events.

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 participant(s) being unaware, and doubleblinding 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 all of the protocol required information to be reported to the Sponsor on each trial participant.

Certified Copy

A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content and structure, as the original.

Clinical Trial/Study

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

Clinical Trial Agreement

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.

Clinical Trial/Study Report

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

Co-Principal Investigator (Co-PI)

A qualified non-clinician scientist or equivalent qualified and experienced person who can provide trial oversight management, and who is jointly and severally liable for the clinical trial.

Comparator (Product)

An investigational or marketed product (i.e. active control), or 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.

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.

Data Monitoring and Safety Board (DSMB)

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.

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 participants' 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 that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see Section 9 "Essential Documents to Conduct a Clinical Trial").

Good Clinical Practice (GCP)

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

Good Manufacturing Practice (GMP)

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

Good Pharmaceutical Practice (GPP)

The commitment to ensure quality service pharmaceutical services for all, and to promote excellence in practice for all that they serve.

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 participant or the participant's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the participant.

Informed Consent

A process by which a participant 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 participant'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 of conducting an official review of documents, facilities, records and any other resources that are deemed by the authority to be related to the clinical trial and that may be located at the site of the trial, at the Sponsor's and/or Contract Research Organization's (CROs) facilities or at other establishments deemed appropriate by the regulatory authority.

Institution (medical)

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

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

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.

Investigator

A person responsible for the conduct of the clinical trial at a trial site

Investigator/Institution

An expression meaning “the Investigator and/or Institution, where required by the applicable regulatory requirements.”

Investigator’s Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human participants.

Legally Acceptable Representative

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

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), GCP and the applicable regulatory requirement(s).

Monitoring Plan

A document that describes the strategy, methods, responsibilities and requirements for monitoring the trial.

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.

National Health Research Ethics Council (NHREC)

The body with the overall responsibility to promote, ensure and monitor compliance by Research Ethics Committees (RECs) in South Africa with relevant legislation, regulations and guidelines. In so doing, the NHREC will accredit and audit the performance of RECs.

Participant

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

Participation Identification Code

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

Pre-clinical Study

Biomedical studies not performed on human participants.

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 Guidance, 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

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 GCP and the applicable regulatory requirement(s).

Quality Control

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.

Randomization

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

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

Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

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 Document

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' 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, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Sponsor

An individual, company, institution or organization that 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 participant. 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, registrars, research fellows).

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).

Validation of Computerized Systems

A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human participant protection and reliability of trial results.

Vulnerable Participants

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

Well-being (of the trial participants)

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