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ATTACHMENT 1: CLINICAL TRIALS SAE FORM

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1. Why Guidelines are necessary

Over the past five years the numbers and complexity of trials have increased significantly, and new and complex issues in trial design have started to present themselves.

HIV vaccine studies pose many scientific and social challenges. Many of the candidate vaccines are novel agents which have no precedent in other licensed vaccines. In addition, many questions remain unanswered about the interpretation of preclinical data, trial design, measurement of efficacy and immunogenicity, and ethical considerations. The complexity of HIV status and the impact it has on individuals and communities adds a dimension unique to HIV vaccine trials. Development of protocols will require a multidisciplinary approach involving virologists, immunologists, molecular and genetics scientists, vaccine manufacturers and public health experts working together.

As sub-Saharan Africa has the most challenging HIV epidemic in the world, there has been a need for a far-reaching clinical trial research agenda to develop products for both the treatment and prevention of HIV. These guidelines are aimed at establishing norms and standards for HIV vaccine trial approval. These guidelines have been developed for use by applicants and by Regulatory Authorities and focus setting standards for HIV vaccine trial applications, in particular, Phase I trials.

1.1. Principles underlying the HIV Vaccine Guidelines

In developing a clinical trial proposal, all the basic rules of good clinical practice must apply. Specifically, applicants are asked to refer to the ICH Guideline on Good Clinical Practice (ICH E6) as well as the South African Guidelines for Good Clinical Practice in the Conduct of Clinical Trials in Human Participants (2000) for a detailed outline of the standards that apply to the conduct of clinical trials.
2. BACKGROUND TO HIV VACCINES

2.1. Overview of HIV Vaccines

Given the unique and complex biological and genetic characteristics of the infectious agent and the absence of a precedent for successful vaccine development against a lentivirus, WHO guidelines are in place to cover some of the approaches used in HIV vaccine development including recombinant derived biological products, on synthetic peptides and on nucleic acid vaccines. However, some of the new approaches to HIV vaccine development such as vectored vaccines are not adequately covered by existing guidelines.

The development of guidelines for the standardisation and control of HIV/AIDS vaccines is more challenging than for other vaccines as the types of immune responses that an effective vaccine should elicit are unknown. For most licensed viral vaccines, serological responses flowing vaccination correlate with vaccine efficacy. For HIV vaccines the measure of efficacy is unknown. The relative importance of humoral immunity and cellular immune responses in measuring vaccine efficacy is unknown, as is the importance of measuring local immune responses at mucosal sites. As a result a variety of vaccine approaches are under investigation, and each product has its own unique challenges of manufacture and potential safety problems.

Apart from the challenges associated with the development and evaluation of candidate vaccines, the design of trials and the ethical considerations associated with all Phases of HIV vaccine development also require special consideration. These trials are likely to be implemented in poor populations who often have limited access to health care and a limited understanding of their rights. Many of the concepts that study participants are required to comprehend before they are to be included in a study, are difficult and alien to people’s thinking. In societies where HIV is still stigmatised, much preliminary work must be undertaken within communities and with individual participants before researchers can be confident that full informed consent can be assured. Once large scale Phase 1 studies are undertaken, the study team must be prepared to respond to the psychological and medical needs of those people who either test HIV positive at screening or who become positive in the course of the trial.

Other issues requiring special consideration include the target population and the inclusion/ exclusion criteria for trials. It is likely that in many developing countries where the HIV epidemic is widespread, future immunisation programmes would focus on high risk populations. At a population level, this would include young adolescents as well as neonates. The question of when and how studies on such populations should be undertaken will require considerable thought. In addition, mass immunisation programmes in high HIV prevalent settings are unlikely to test individuals for HIV before they are immunised. Safety studies in HIV infected individuals will also be required at an early stage of the vaccine development process.

Whilst the reporting of adverse drug events is essential in all clinical trials, the novel nature of HIV vaccines necessitates significant attention to adverse
event reporting. Specific definitions and guidelines must be developed, and the manner in which vaccines are monitored in both the short term and long term must be clearly described.

2.2. HIV Vaccine categories

For the purpose of these guidelines the following categorisation of candidate vaccines has been adopted from the WHO UNAIDS Consultation on the Regulation and Clinical Evaluation of HIV/AIDS Preventive Vaccines. Different vaccine categories pose different potential risks to vaccines. Trial design and safety monitoring must reflect the potential safety concerns anticipated with the different vaccine formulations. The following section outlines these vaccine categories and some of the anticipated challenges with each of the technologies. Current thinking advises caution about approving trials of live attenuated vaccines.¹

2.2.1. Inactivated Vaccine

Complete inactivation of any biological activity must be ensured, as well as the safety of the cell substrate, be they continuous cell lines or primary cell cultures.

2.2.2. Recombinant Protein Vaccines

In the case of HIV vaccines based upon HIV regulatory proteins e.g. Tat protein, the potential toxicity of protein should be considered. The second issue is the need to ensure comparability and consistency of production so that the vaccine materials used in the definitive clinical trials should be fully characterised and specified and shown to be capable of consistent lot to lot production.

2.2.3. Recombinant DNA Vaccines

A key issue with recombinant DNA vaccines is the biological activity of the transgene expressed by the vaccine. This is relevant whether it be a viral regulatory gene such as tat that is known to have toxic effects in vitro or an immunomodulatory gene co-expressed with a viral antigen to enhance anti-HIV responses.

2.2.4. Recombinant Viral Vector Vaccines

There are currently no biologicals based upon viral vectors licensed for use as preventive vaccines in humans. Regulatory issues associated with this approach have been addressed in documentation produced by the FDA and EMEA with regards to gene therapy. Of particular importance with this vaccine technology is the cell substrate employed. This is particularly relevant in the

²WHO guidelines for vaccine clinical trial regulation.
situation where replication defective viruses are delivered because many of
the helper cell lines used to produce the viral structural protein used to
package the viral nucleic acid are derived from continuous cell lines that may
be tumorigenic.

2.2.5. Recombinant Bacterial Vector Vaccines

Vectors based upon attenuated mycobacterium, such as BCG vaccine or on
attenuated *Salmonella* strains are being explored in HIV/AIDS vaccine
development. Guidelines for this type of product will be required.

2.2.6. Life Attenuated HIV Virus

There are serious concerns and reservations about the development of live
attenuated HIV vaccines, particularly given the current limitations of
knowledge on the biology and genetics of HIV in relation to virulence and
attenuation. Studies in model systems have so far failed to disassociate the
pathogenic potential of HIV (or SIV) from its replicative capacity *in vivo*, ie.
there are no specific genes for pathogenicity of HIV *in vivo*. Moreover, the
degree of vaccine induced protection appears to correlate with the replicative
capacity of the virus. As this vaccine approach provides potent vaccine
protection in model systems, it remains a valuable tool in laboratory research,
but considerable further work would be required before it could be considered
appropriate for clinical studies.

3. REQUIRED CONTENTS OF HIV VACCINE TRIAL PROPOSALS

Trials will be evaluated according to the following:

**Clinical Trial Checklist:**

a) Title & Summary
b) Study sites
c) Investigators: describing experience in the conduct of clinical trials and
   in HIV/AIDS trials
d) Responsibilities of trial staff: Description of the relative responsibilities
   of all senior trial staff, and of laboratory staff
e) Identification of site PIs and National PIs: Where more than one site is
   being used for a study, a national PI must be identified.
f) Background rationale to the Vaccine
g) Preclinical data: animal toxicology and immunogenicity and laboratory
   evaluation including potency testing where possible
h) Summary of Product characteristics
i) Prior human experience with vaccine, insert or vector.

3.1. Manufacturing and GMP

a) Testing and release criteria: Description of safety data sheets, cell
   characterization, and medium constituents.
b) Scale-up potential
c) Stability & storage
d) Adjuvants
e) Physical interactions between vaccine components, container and dose delivery system.
f) Waste disposal for test material.

3.2. Primary & Secondary objectives
3.3. Study design

a) Selection of site and rationale
b) Site preparation and capacity
c) Community preparation
d) Recruitment
e) Screening
f) Enrollment
g) Informed consent procedure
h) Study Population Inclusion & exclusion criteria
i) Handling & allocation of vaccine
j) Vaccine delivery
k) Randomization where appropriate
l) Follow-up
m) Safety monitoring and AE and SAE reporting
n) Access of study participants to researchers and to emergency care

3.4. Laboratory testing and specimen handling and storage

a) Good Laboratory Practice

3.5. Statistics section with explanation
3.6. GCP Monitoring of the trial
3.7. Ethics monitoring of the trial
3.8. Timetable
3.9. Ethical approval
4. PHASE I HIV VACCINE TRIAL GUIDELINES

4.1. Introduction

This section will outline the requirements for a HIV vaccine Phase I trial. These trials are concerned with HIV vaccine formulations with no or proven limited proven human tolerability data. Review of all relevant pre-clinical and clinical data is important.

4.2. Definition of Phase I clinical studies

The primary objective of a phase 1 study is to:

- Establish preliminary safety and tolerability of different vaccines, when administered through a given route and at a specified dosage.

The secondary objectives could include:

- Qualitative determination of Immunogenicity measurements,
- Characterisation of any HIV infection that occurs subsequently within the trial period
- Preliminary data on patient acceptability.

4.3. Requirements for Trial materials

The following items of information will assist in providing assurance that the quality concerns have been met. The reviewer may request additional information where the applicant has given insufficient or inconsistent information.

b) Qualifications of personnel responsible for manufacture, quality assurance, quality control and final product release
c) Manufacturing site: Address and location of each site of manufacture, processing, packaging, storage, test laboratories and animal facilities used for this product. Some information regarding: layout, finishes, HVAC, product flow, containment, other activities in the same facility and arrangements to prevent contamination of the product.
d) Information on the implementation of documentation: Standard Operating procedures, Change Control Procedures etc.
e) Raw materials: Derivation, maintenance and testing of all organisms and constructs
f) Derivation, maintenance and testing of production cell substrates
g) Key raw materials and animal or human derived materials used in the process
h) Specifications and tests of all materials which are included in the final formulation.
i) Specifications and tests of materials used during subsequent processing; e.g. chromatography media and reagents, including methods of regeneration and storage.
j) Available toxicity data on all materials used during processing and final formulation.
k) Specifications of trial material containers and closures.
l) Current validation information.
m) Manufacturing methods

- Narrative description with specific reference to deviations from the developmental methods and their justification
- Description and/or specifications of equipment used
- Flow chart showing process steps, sample points and in-process tests.
- Methods and validation of removal of materials used in preparation.
- Filling, freeze-drying and packaging methods

n) Final product

- Quantities of all constituents in the final product formulation (including traces)
- Specifications for the final product including the upper and lower limits for results and specifications.
- Specifications for the trial material container and closure. Evidence for suitability.
- Packaging processes, Labelling, transport and storage
- Batch manufacturing records for trial and other recent production lots, made in accordance with the method described in the current protocol.

4.4. Stability

There must be data that demonstrate the stability of the product in the final container and its closure, over the proposed time of the trial. Where strict environmental control during storage, transport and use of the trial material is not possible a documented program that collects and tests field samples, at all trial sites, to demonstrate that this stability has been achieved during the trial may be required.

4.5. Safety of Vaccine Material

These should be specified on the protocol and include:

a) Measures to ensure cold-chain maintenance and storage
b) Evidence that the product to be used for the trial is identical in specifications and manufacture to material that has been used in preclinical testing and earlier phases of clinical trials. Where there is uncertainty, this should be described, and the reasons for the changes explained.
c) A description regarding disposal of waste and unused product as well as compliance with relevant laws and regulations.

5. PRECLINICAL DATA

5.1. Preliminary Potency

Where relevant vaccine development should establish preliminary potency tests which will be used for routine batch release. Although the potency assay should mimic the human clinical function of the vaccine in humans. In phase I trials an assay based on artificial measures reflecting potential clinical protection maybe used. The nature of the assay will be determined by the nature of candidate vaccine material. In some instances such as polysaccharide vaccines, chemical characterisation may be sufficient. Whilst in those products where little is known about the pathogenic mechanism and or protective factors, animal testing with subsequent serologic evaluation or challenge testing is informative. As the understanding of the mechanism of protection and immunity to vaccine progresses, every effort should be made to replace in vivo potency assays with validated in vitro alternatives based on the biological activity of the product, test systems or novel laboratory methods as they become available.

5.2. Immunogenicity

Currently there is no effective HIV vaccine necessitating the continued use and evaluation of controlled animal models to evaluate the potential for an immunised subject to control virus replication. Furthermore animal models have yielded conflicting observations on the efficacy of specific vaccine strategies. Models currently in use include transgenic and immunodeficient mice. Common primate models used are the HIV-2 or SIV model. Animal immunogenicity data inform the selection of doses, schedules and routes of administration to be evaluated in clinical trials. Preclinical studies should be designed to assess the relevant immune responses, e.g., seroconversion rates, geometric mean antibody titres, or cell-mediated immunity in vaccinated animals. Such studies may also address interference between antigens and/or live viruses. If a vaccine consists of more than one antigen, the response to each antigen should be evaluated.

Immunogenicity studies may include the characterisation of antibody class, avidity, affinity, half-life, memory, and potential induction of cell mediated immunity as well as release of soluble mediators affecting the immune system as appropriate.

The evaluation of immunogenicity models during phase I clinical trial studies are encouraged in order to develop a clearer understanding of vaccination responses.

Whilst immunogenicity testing in animals maybe necessary during vaccine development to demonstrate an ability to induce an appropriate immune response, an animal immunogenicity test may not be needed for routine lot release.
5.3. In vitro and toxicology data

Animal toxicity studies must be performed to assess potential toxic effects of a vaccine in target organs, including the haematopoietic and immune systems as well as to assess systemic toxicity. These toxicity studies may identify potential toxicity problems that would require further clinical monitoring. It is recognized that there may not be a suitable animal model for the toxicological evaluation of the candidate vaccines. Furthermore available models may not predictive of human responses. Often interpretation of animal toxicity data can be difficult.

Repeat dose toxicity tests will only be required in those vaccine dose regimens / composition that require it. The design and value of repeated dose toxicity testing should therefore be considered on a case by case basis.

If a vaccine is intended to be clinically tested in women of childbearing age, the need for reproductive toxicity studies and studies of embryo/foetal and perinatal toxicity should be considered on a case by case basis. Reproductive toxicity studies will need to be undertaken in any case before licensing.

Toxicity tests include:

a) Evaluation of a safe initial dose and subsequent dose escalation schemes.
b) Evaluation of single \{ or repeat doses as appropriate \}
c) Determination of a relevant set of safety parameters for clinical monitoring
d) Demonstration of potential reversibility of virulence of attenuated vaccine strains
e) Demonstration of completeness of inactivation of inactivated vaccine strains
f) Demonstration of completeness of inactivation as well as reversibility to toxicity of toxoids
g) Local tolerability studies, and
h) Evaluation of the potential of the vaccine antigen(s) to induce antibodies cross-reactive with human tissues, on a case by case basis (e.g. Streptococcal vaccine).

Preclinical safety studies should include a demonstration of adequate attenuation of live organisms or a demonstration of effective inactivation of killed organisms. Where different routes of administration are proposed, multiple safety/ toxicity studies should be considered in a suitable animal model addressing specific safety concerns associated with vaccine administration via each routes. Caution should be used when extrapolating safety data obtained using one route of administration to other routes.
6. TRIAL CONDUCT

6.1. Trial design

The basic requirements of each trial are outlined in Section 3. Certain aspects of trial design which are special to Phase I studies are emphasised in this section. The prime objective of Phase I studies is tolerability and safety. For this reason Phase I HIV vaccine trials:

a) Ordinarily involve a small number of low risk, healthy human subjects (about 20) per regimen. This number will determine the true occurrence of common adverse events at greater than 20% and will identify other adverse events. If the objectives of the trial are other than safety as defined here then the sample size must be calculated accordingly.

b) May be open labelled or controlled.

c) Simultaneous trials involving different routes of administration will be considered on merit. Where this is proposed, the route thought to be safer should be assessed first. Where different dosage regimens are being evaluated the safety of the lower dose should be established before a different dose is evaluated. The time period between each dose intervention must be justified in terms of preclinical and clinical data. The management of the groups receiving different regimens should be clearly described to ensure that no confusion in the conduct of the trial can occur.

d) Where a vaccinee is to receive repeat immunisation the period between successive doses should be justified.

e) Where different regimens are being evaluated and different sites are participating in the study, it is preferable that each site evaluates a different regimen rather than splitting study participants for one regimen across two or more sites.

f) Safety reports should be submitted to the Regulatory Authority at approved intervals.

g) Appropriate laboratory testing before enrolment and inclusion. This should include screening of all basic haematological and biochemical parameters to ensure that participants are healthy, and allow appropriate monitoring after vaccination.

h) Where women subjects are participants, pregnancy must be excluded and appropriate contraception must be employed. Men should also be advised to use contraception with their partner. The duration of contraceptive use should be specified and should be justified.

i) Safer sex counselling must be given to all participants irrespective of their low risk status.

j) HIV pre and post test counselling must be offered with appropriate referral for those testing positive both at screening and during the course of the trial.

k) Informed consent procedures and the patient information leaflet must be described

l) Ensure subject safety as specified under safety monitoring
6.2. Safety Monitoring

Safety monitoring is always important in the conduct of clinical trials, but the novel technology used in many of the HIV candidate vaccines requires particular attention when it comes to safety monitoring. The elements of safety monitoring during clinical trials can be categorised as follows:

a) Preclinical data and other laboratory and manufacturing data to identify anticipated risks of harm should be included. Anticipated risks depend on the type of HIV vaccine being studied (see section 2.2.). Where possible the description should include the risk factors, the anticipated severity and their likely frequency. These should be adequately referenced and preferably supported by animal studies.
b) Details of toxicology studies should be included. This should include risks associated with adjuvants and additives.
c) Systems and methods for detection of adverse events must be described.
d) Where patient diaries are utilised local validation must be provided.
e) Methods employed to assess adverse events and their clinical significance should be described.
f) Procedures must be in place to minimise the risk of harm

g) Measures must be taken to manage anticipated risks of harm

h) A communication plan for informing relevant players of any new safety information must be described.

6.3. Detection of Adverse Events

Due to the public health implications of these clinical trials, more urgent reporting timelines are required than for other clinical trials. All serious adverse events (SAEs) both expected and unexpected should be reported to the Regulatory Authority and the Research Ethics Committee within 24 hours of notification to the applicant. Non serious adverse events should be reported at a monthly interval unless is it considered to be a potential new signal or of clinical importance. The reporting time frames and format are further described in the draft Guidelines on Regulating the Conduct of Clinical Trials in Human Participants. A copy of a model SAE report form is attached (Attachment 1)

The following monitoring parameters for adverse events should be considered. For each parameter timelines and an appropriate level of monitoring should be specified.. The Case Record Form should be designed to capture all adverse events.

a) Local toxicity at the injection site
b) Systemic symptoms
c) Haematological: CBC with differential, platelets
d) Immunology: CD4 and CD8 lymphocyte number and percentage
e) Hepatic profile
6.4. Assessment of Adverse events

All reported serious adverse events should be described in detail, including information on possible underlying disease, concomitant vaccinations or drugs, actions taken and outcome. The possibility of a causal relation with the vaccination should be considered and investigated in every case. However, attributing causality is often difficult, especially when the event occurs in the background of the trial population. It should be considered whether the adverse event is sufficiently serious as to require suspension of product development, or whether additional clinical safety studies may be needed to confirm the relationship between the vaccine and the event, and more rigorously to establish incidence. Investigators should be appropriately trained in reporting adverse events, investigating such events and assessing causality of adverse events, particularly relating to vaccines. The following pointers must be considered:

a) If the vaccine consists of more than one antigen the response to each antigen should be evaluated.
b) The causality criteria should be appropriate for vaccines.
c) The trial must allow for lot-specific assessment of adverse events.
d) Adverse events should be described and analysed according to system organ class.
e) Plans to follow-up study subjects in the medium (up to one year) and long term (beyond 1 year) should be described.
f) A data safety monitoring board must be in place and the members’ terms of reference, composition, function and remuneration by the sponsor should be clearly defined. There reviewing procedures should be described at the outset of the trial.

6.5. Trial Monitoring

All protocol amendments must be approved. The applicant must report all protocol deviations and violations and other breaches of Good Clinical Practice to the Research Ethics Committee and the Regulatory Authority.

6.6. Management and Prevention of Serious Adverse Events

a) Treatment guidelines must be in place for expected or anticipated risks of harm.
b) All investigators and study staff need to be trained in how to detect, manage and report SAEs and AEs – this includes updated training on new risks as they arise.
c) Measures must be in place to ensure that study participants have 24-hour access to care if an adverse event is experienced.

d) An investigator must be available and accessible to study subjects at all times during the entire study period.

e) A monitoring procedure should be in place as mentioned above for early detection of adverse events.

f) Procedures must be in place for handling new risks identified during the study. These must include treatment of the patient, changing trial conditions, suspending a vaccine lot, investigating and communicating results of investigations, amending investigator’s brochure and consent form etc.

g) Procedures for waste disposal and disposal of unused product must be described.

h) Procedures for conducting a thorough investigation of serious adverse events must be described.

i) Procedures to take a drug and medical history at each follow-up visit must be in place.

6.7. Communication of Serious Adverse Events

The applicant must provide clear timelines and procedures for communicating new risks to investigators, subjects, the Regulatory Authority, the Research Ethics Committee, the sponsor and the public where applicable.

6.8. Trial monitoring

Independent monitoring for trial conduct and ethics must be specified. These include:

a) Independent GCP monitoring.

b) Data safety monitoring board.

c) Independent ethics monitoring.
7. THE ETHICAL CONDUCT OF HIV VACCINE TRIALS

7.1. Introduction

Ethics remains the primary responsibility of local Research Ethics Committee. These guidelines provide a framework to guide applicants on some of the important ethical considerations which should be addressed in their study design. The Regulatory Authority will not approve a HIV vaccine trial application until the applicant has obtained approval from their local Research Ethics Committee. Where concerns have been identified by the Regulatory Authority, these will be addressed to both the applicant as well as the ethics committee. The response from the ethics committee will guide the final decision as to whether the trial is deemed ethical or not.

7.2. General

The trial must be designed and executed in accordance with the internationally accepted guidelines on Good Clinical Practice (GCP) (e.g ICH E6 GCP Guidelines, SA GCP Guidelines); and deviations from this general standard must be motivated. Approval must have been obtained by a local ethics committee accredited with the national ethics body once a process for accreditation is in place.

7.3. Conduct of the research

   a) The knowledge sought cannot be obtained by any other practicable method, the clinical study is relevant, and the study rationale is relevant.
   b) The suitability of the study application in relation to the objectives of the study; i.e. the potential for reaching sound conclusions with the smallest possible exposure to risk of participants, and the justification of predictable risks and inconveniences weighed against the anticipated benefits for the participants and/or others.
   c) If the trial is not performed in the country of the sponsor, an explanation for this must be given. The rationale for this question is to ensure that exploitation of vulnerable populations is not taking place
   d) Screened applicant and participant privacy and confidentiality must be ensured.

7.4. Members of the research team and trial sites

   a) Principal investigators (PI’s) and participating investigators must be sufficiently competent and qualified to conduct trials, and evidence thereof must be provided through relevant documentation
   b) Investigator(s) must have sufficient availability to conduct this particular trial, taking into account also the number of clinical trials they are conducting or involved with.
   c) A Coordinating Investigator must be identified for a multi-site study in the country.
   d) Investigator(s) must be registered with the appropriate Professional Regulatory bodies.
e) Investigator(s) must have undergone GCP training.
f) Investigator remuneration and accounting thereof must be adequately described. Justification must exist if it is very high or very low.
g) A qualified physician, who may be the PI or sub-investigator for the trial, must be responsible for all trial-related medical decisions for the duration of the trial, the investigator/institution must ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial.
h) Care of subjects after the duration of the trial will be in accordance with the standard of care as determined by the national ethics committee.
i) There must be appropriate facilities and capacity at the trial site to conduct the trial, taking into account also the number of studies currently performed at the site, the number of staff involved in the studies, and access to emergency medical treatment at the site.
j) Strategies must have been implemented to ensure that trial capacity develops especially for practitioners from the disadvantaged groups.
k) Community preparation must be described, as must the process of recruiting participants from the community. Information sheets, workshop guidelines or advertisements which are used for this purpose, must be submitted to the Regulatory Authority for approval.

7.5. Study population

a) Participants recruited in phase must be able to understand the implications of participating in Phase I HIV Vaccine trials.
b) Steps must be taken to promote equality in recruitment for and conduct of the trial within the scientific parameters of trial design.
c) Conditions which may adversely impact on marginalisation and vulnerability of participants, within the requirements for a Phase I, must be adequately addressed and these measures must be adequately described in the protocol and/or application.
d) Phase I participants must not be at high risk of contracting HIV and this must be described by the protocol.
e) Where the nature of the trial material merits it, mechanisms for individualized long-term follow-up of participants and children they may subsequently produce must be clearly described and incorporated into the protocol and/or application.

7.6. Community participation

Adequate provision must have been made for meaningful community participation, including broader community representation, in an early and sustainable manner, in the relevant aspects of the research, including recruitment strategies, design, development, implementation and distribution (including publication) of results.
7.7. Informed consent

a) Legal requirements for informed consent must be met and special measures must be taken to protect persons who may be limited in their capacity or ability to give consent, including in their language and their level of education.

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

c) Both the informed consent discussion and the written informed consent form and other written documentation to be provided to participants should include explanations of those issues that are relevant to a Phase I HIV vaccine trial.

d) The content of the information given to research participant must be sufficient, and the process must be designed to ensure understanding of potential study participants.

e) All identified foreseeable risks including potential physiological and psychosocial risks, any additional risks, as well as the possibility of unforeseen risks, must be explained and understood by participants.

f) Risk minimisation measures are adequately provided for each participant, and they include, but are not limited to:

  g) Counselling against the belief that the trial vaccine will necessarily afford protection.

  h) Appropriate and ongoing i.e. after the termination of the official study period, monitoring, referral, and support for trial related social harm or trial related stigma and discrimination, including ongoing access to legal and appropriate support, such as by an ombudsperson.

  i) Provision of free HIV testing which can distinguish between infection with HIV and an anti-body response to the trial vaccine that could lead to “false positive” testing on the standard ELISA test and which is not caused by infection with HIV, for as long as “false positivity” may persist.

  j) Provision of a voluntary trial identity card in order to secure assistance including access to free differential testing provided by the life insurance industry to facilitate access to insurance.

  k) Adequate steps to ensure privacy and confidentiality of information and trial participation.

  l) The informed consent agreement clearly recording the provision of insurance and indemnity to cover the liability of the investigator and sponsor(s).

m) Benefits to participants and broader communities, as explained below, must be adequately imparted to and understood by the participants.
7.8. Benefits

a) Reimbursement of expenses and token compensation for inconvenience or discomfort, that is reasonable and balanced in the context of phase I trials, must be paid to trial participants.

b) Measures must be indicated to ensure that certain predetermined benefits will accrue to the broad phase I participant community, whether the trial vaccine is licensed or not.

These measures must include but are not limited to:

- Sharing of research results (whether positive, negative or indeterminate) as soon as it is appropriate.
- Capacity building of community members
- Increased knowledge of general HIV prevention strategies.

7.9. Risk reduction of HIV infection during study period

Risk reduction counselling regarding risks of HIV-infection during the trial and access to prevention methods to minimise HIV infection during the trial must be provided to all participants, with information of new methods and new methods to be added as they are discovered and validated. Such counselling ought to be appropriate to the community and achievable within the trial infrastructure.

7.10. Reinforcing informed consent and HIV prevention strategies

Adequate plans for maintaining informed consent, including risk reduction, must be in place.

7.11. Care and treatment

a) Responsibility for the overall care of participants must be clarified between the researchers and the public health sector.

b) Referral and support services must be provided for those who screen positive before the trial begins in accordance with the provisions in the standard of care guidelines established by the national ethics committee.

c) Similar provisions must be made for the adequate provision of care and treatment for non-HIV, possible trial sequelae, including vector related toxicity and infection, tumorigenic complications, general reproductive health effects, nutritional changes or problems, allergic reactions, the possibility of germ line indications and genetic counselling that may be indicated with regard to certain vaccines.
7.12. Conflicts of interest and multiple trials

a) Participants on Phase I HIV Vaccine trial should not participate concurrently in any other clinical trial.
b) Consideration must be given to the capacity of the specific trial site to conduct this trial, in light of factors such as capacity and multiple trials at the same site.

7.13. Pregnancy

Adequate precautions must be taken that pre-existing pregnancy and the subsequent occurrence of pregnancy during the trial is excluded in this phase I trial.

7.14. Trial Monitoring

Independent Ethics monitoring is recommended, which ought to include measurement of the informed consent process.
ATTACHMENT 1

DRAFT CLINICAL TRIAL SERIOUS ADVERSE EVENT/REACTION REPORTING FORM

- Complete in English
- Refer to Reporting Guidelines for advice on reporting
- When reporting dates report as (dd/mm/yy) - Indicate estimated dates with an asterisk (*)
- Submit SAE reports to: Regulatory Authority (address)
- Fax: Tel:

<table>
<thead>
<tr>
<th>SAE # ____________________</th>
<th>Study Reference # ____________________</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Patient Initials:</th>
<th>Sex (Mark with X)</th>
<th>Study Design (mark with X)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MALE FEMALE</td>
<td>Open Single Blind Double-Blind</td>
</tr>
</tbody>
</table>

| Race: | Date of Birth
Or age at event | Development Phase of trial |
|-------|-----------------|-----------------------------|

<table>
<thead>
<tr>
<th>Weight at time of event: ____ kg</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Height at time of event: ____ cm</th>
<th>Randomisation No.</th>
</tr>
</thead>
</table>

2.

<table>
<thead>
<tr>
<th>Investigator name: __________________________</th>
<th>Phone #: __________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Site Address: __________________________</td>
<td>Email: __________________________</td>
</tr>
<tr>
<td>City: __________________________</td>
<td>Postal code: __________________________</td>
</tr>
<tr>
<td>Province: __________________________</td>
<td>Study Site Reference Number: __________________________</td>
</tr>
<tr>
<td>Sponsor Name: __________________________</td>
<td>__________________________</td>
</tr>
</tbody>
</table>

3.

Investigational Medicines History

<table>
<thead>
<tr>
<th>Name of study medication</th>
<th>Causality (see below)</th>
<th>Medicine Identity known? Y/N</th>
<th>Dose &amp; Frequency</th>
<th>Route</th>
<th>Start Date</th>
<th>Stop Date (Mark X if ongoing)</th>
<th>Indication for use</th>
</tr>
</thead>
</table>

* Causality: 1=Definite, 2=Probable, 3=Possible, 4=Unlikely, 5=Unknown

4.

Concomitant Medicines History (Non-Investigational concomitant Medicines)

Asterisk any suspected medicines

<table>
<thead>
<tr>
<th>Name of medication</th>
<th>Causality* (see below)</th>
<th>Dose &amp; Frequency</th>
<th>Route</th>
<th>Start Date</th>
<th>Stop Date (Mark X if ongoing)</th>
<th>Indication for use</th>
</tr>
</thead>
</table>

* Causality: 1=Definite, 2=Probable, 3=Possible, 4=Unlikely, 5=Unknown
5. **Adverse Event Terms (reported terms):**

<table>
<thead>
<tr>
<th>Onset Date:</th>
<th>Improved/Resolved?</th>
<th>Yes</th>
<th>No</th>
<th>N/a</th>
<th>If Yes enter Date:</th>
</tr>
</thead>
</table>

6. **Event Description: (including dates of hospitalisation)**

__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________

If necessary please continue event description on Supplementary Information Sheet [ ] Mark (x) if used

7. **Why was the event serious (mark ALL that apply (X))**

<table>
<thead>
<tr>
<th>Why was the event serious</th>
<th>Outcomes at the time of the report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal</td>
<td>Resolved/Improved</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>Recovered with long term sequelae</td>
</tr>
<tr>
<td>New/prolonged in-patient hospitalisation</td>
<td>Condition worse</td>
</tr>
<tr>
<td>Persistent or significant disability/incapacity</td>
<td>Not available</td>
</tr>
<tr>
<td>Congenital anomaly / birth defect</td>
<td>Fatal</td>
</tr>
<tr>
<td>Medically significant</td>
<td>If Outcome was Fatal: Date of Death: _____________</td>
</tr>
<tr>
<td>Required intervention to prevent one of the above outcomes</td>
<td>Cause of Death: _________________________________</td>
</tr>
</tbody>
</table>

8. **Treatment of Event:** [ ] Yes, described below  [ ] None  [ ] Unknown

Description of treatment: ___________________________________________________
__________________________________________________________________________

9. **Relevant laboratory/diagnostic tests:** [ ] Yes, described below  [ ] None  [ ] Unknown

<table>
<thead>
<tr>
<th>Date</th>
<th>Test</th>
<th>Results</th>
<th>Mark (X) if Pending</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10. Relevant Medical History - continue on Supplementary Information Sheet

<table>
<thead>
<tr>
<th>Date</th>
<th>Disease / Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Signature (reporting Investigator)

<table>
<thead>
<tr>
<th>Name:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title:</td>
</tr>
<tr>
<td>Phone No:</td>
</tr>
<tr>
<td>Fax No:</td>
</tr>
<tr>
<td>Date:</td>
</tr>
</tbody>
</table>

11. CLINICAL TRIAL SERIOUS Adverse Event (SAE) REPORTING FORM

**SUPPLEMENTARY INFORMATION**

Please indicate the section to which supplementary Information refers:

<table>
<thead>
<tr>
<th>Reporting Investigator (Print Title and Name):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telephone Number: ___________________________</td>
</tr>
<tr>
<td>Fax Number: ________________________________</td>
</tr>
<tr>
<td>Signature: __________________ Date: ___________</td>
</tr>
<tr>
<td>For Official Use Only:</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Protocol Reference #:</td>
</tr>
<tr>
<td>Date Received:</td>
</tr>
<tr>
<td>Date Reviewed:</td>
</tr>
<tr>
<td>Recommended Action:</td>
</tr>
</tbody>
</table>
Introduction:

The elements of safety monitoring during clinical trials can be categorised as follows:

1) Preclinical data and other laboratory and manufacturing data to **identify anticipated risks** of harm.
2) Systems and methods for **detection** of adverse events.
3) Methods employed to **assess** adverse events detected and their clinical significance.
4) Procedures in place to **minimise** the risk of harm
5) Measures taken to **manage** anticipated risks of harm
6) A **communication plan** for informing relevant players of any new safety information.

The following points have been included for consideration during evaluation of safety parameters for HIV vaccine clinical trial submissions:

1) **Background data:**

1. Safety must be a primary or secondary objective in all studies regardless of Phase of trial.
2. Have the anticipated risks been described? Description should include (where possible) the anticipated severity, frequency and risk factors.(adequately referenced and preferably supported by animal studies). This should include risks associated with adjuvants and additives as well. Anticipated risks depend on the type of vaccine being studied:
a. **Inactivated Vaccines:**

Has the complete inactivation of any biological activity and the safety of the cell substrate, be they continuous cell lines or primary cell cultures been ensured?

b. **Recombinant protein vaccines:**

Has consistency of lot-to-lot production been ensured?

Where relevant, has the potential toxicity of HIV regulatory proteins e.g. Tat protein been carefully considered?

c. **Recombinant DNA vaccines**

A key issue with recombinant DNA vaccines is the biological activity of the transgene expressed by the vaccine. This is relevant whether it be a viral regulatory gene such as tat that is known to have toxic effects *in vitro* or an immunomodulatory gene co-expressed with a viral antigen to enhance anti-HIV responses.

d. **Recombinant viral vector vaccines:**

There are currently no biologicals based upon viral vectors licensed for use as preventive vaccines in humans. Regulatory issues associated with this approach have been addressed in documentation produced by the FDA and EMEA with regards to gene therapy.

Of particular importance with this vaccine technology is the cell substrate employed. This is particularly relevant in the situation where replication defective viruses are delivered. Many of the helper cell lines used to produce the viral structural protein used to package the viral nucleic acid are derived from continuous cell lines that may be tumorigenic.

e. **Recombinant bacterial vectors**

Vectors based upon attenuated mycobacterium, such as BCG vaccine or on attenuated *Salmonella* strains are being explored in HIV/AIDS vaccine development. Guidelines for this type of product will be required.

f. **Live attenuated HIV virus**

There are serious concerns and reservations about the development of live attenuated HIV vaccines, particularly given the current limitations of knowledge on the biology and genetics of HIV in relation to virulence and attenuation. WHO states that “studies in model systems have so far failed to disassociate the pathogenic potential of HIV (or SIV) from its replicative capacity *in vivo*, i.e. there are no specific genes for pathogenicity of HIV *in vivo*. Moreover, the degree
of vaccine induced protection appears to correlate with the replicative capacity of the virus. As this vaccine approach provides potent vaccine protection in model systems, it remains a valuable tool in laboratory research, but considerable further work would be required before it could be considered appropriate for clinical studies.”

3. Have the relevant toxicology studies described in the protocol?

“Toxicity studies in animals should be undertaken to assess the potential toxic effects of a vaccine in target organs, including the hematopoietic and immune systems as well as to assess systemic toxicity. Toxicity studies may help to identify potential toxicity problems requiring further clinical monitoring. Detailed guidance on toxicological and pharmacological testing may be found in EMEA Note for Guidance on preclinical pharmacological and toxicological testing of vaccines (15). However, it should be recognized that a suitable animal model may not be available for undertaking toxicological evaluation of candidate vaccines and that such models are not necessarily predictive of human responses. Interpretation of data could be difficult. Furthermore, classical repeated dose toxicity test as applied to medicines may not be applicable for vaccines, since there is no chronic exposure of the subject to a vaccine through repeated administration.

The design and value of repeated dose toxicity testing should therefore be considered on a case by case basis, as should be the selection of animal species used for these investigations. If a vaccine is intended for use in women of childbearing age or during pregnancy, reproductive toxicity studies and studies of embryo/foetal and perinatal toxicity are necessary.

**Toxicity tests may include:**

a) an evaluation of the initial safe dose and subsequent dose escalation schemes relevant to the clinical dose  
b) an evaluation of single and repeat dose as appropriate  
c) a determination of a relevant set of safety parameters for clinical monitoring  
d) a demonstration of potential reversibility to toxicity of toxoids or inactivated antigens  
e) local tolerance studies, and  
f) an evaluation of the potential of the vaccine antigen(s) to induce antibodies cross-reactive with human tissues.

Preclinical safety studies should include a demonstration of adequate attenuation of live organisms, or a demonstration of effective inactivation of killed organisms, as appropriate. Where different routes of administration are proposed, multiple safety/toxicity studies may have to be conducted in a suitable animal model addressing specific safety concerns associated with vaccine administration via each routes. Caution should be used when extrapolating safety data obtained using one route of administration to other routes.”

4. Have the Laboratory and Manufacturing procedures which ensure safety of the antigen, vector, adjuvants and additives been described?

---

2 Derived from the WHO Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations.
5. Have the results of clinical data from other studies previously conducted or ongoing concurrently (for all phases – especially II and III) been reviewed?
6. Route of administration and safety measures taken to ensure safe administration (e.g. retain cold chain and aseptic technique and staff appropriately trained)

2) Detection of Adverse Events:

1. Is the format and timeframes for reporting adverse events in line with the Regulatory Authority guidelines?

   - Due to public health implications of these clinical trials, more urgent reporting timelines than is normally required for other clinical trials:
   - Serious events (expected and unexpected) – within 24 hours of notification to the applicant sent to the Regulatory Authority and REC.
   - Nonserious adverse events as line-listing – at a monthly interval unless is it considered to be a potential new signal or of clinical importance.

   - The reporting time frames and format are further described in the Draft Guidelines on Regulating the Conduct of Clinical Trials in Human Participants.

   - A copy of a model SAE report form is attached and could be made available to applicants as requested.

2. Are monitoring parameters for the following adverse events in place?

   - Local toxicity at the injection site
   - Systemic symptoms
   - Haematologic: CBC with differential, platelets
   - Immunologic: CD4 and CD8 lymphocyte number and percentage
   - Hepatic function
   - Renal function
   - Dermatologic function,
   - Neurologic function
   - GI function
   - Social impact (e.g. difficulty obtaining insurance, foreign travel, appearance of HIV positive screening test)
   - Other unexpected adverse events

3. Are the timelines for monitoring the above-mentioned safety parameters in place and are they appropriate?
4. Is the case record form for adverse events appropriate and complete?
5. Have procedures for conducting a thorough investigation of serious adverse been described?
6. Are there procedures in place to take a drug and medical history at each follow-up visit?

3) Assessment of Adverse events
The purpose of proper assessment of risks is succinctly described in the WHO guidelines for vaccine clinical trial regulation.

“All reported serious adverse events should be described in detail, including information on possible underlying disease, concomitant vaccinations or drugs, actions taken and outcome. The possibility of a causal relation with the vaccination should be considered and investigated in every case. However, attributing causality is often difficult, especially when the event occurs in the background of the trial population. It should be considered whether the adverse event is sufficiently serious as to require suspension of product development, or whether additional clinical safety studies may be needed to confirm the relationship between the vaccine and the event, and more rigorously to establish incidence.”

1. If the vaccine consists of more than one antigen the response to each antigen should be evaluated.

2. Have the investigators been appropriately trained in reporting adverse events, investigating such events and assessing causality of adverse events, particularly relating to vaccines?

3. Does the trial allow for lot-specific assessment of adverse events?

4. Will adverse events be described and analysed according to system organ class?

5. What are the applicant’s plans to follow-up study subjects in the medium (up to one year) and long term (beyond 1 year)?

6. Is there a data safety monitoring board in place? Are the members’ terms of reference, composition, function and remuneration by the sponsor clearly defined?

**Trial Monitoring:**

1. Has the applicant agreed to report all protocol deviations and violations and other breaches of Good Clinical Practice to the REC and Regulatory Authority?

4) **Management and Prevention:**

1. Are treatment guidelines in place for expected or anticipated risks of harm?

2. All investigators and study staff need to be trained in how to detect, manage and report ADRs – this includes updated training on new risks as they arise.

3. Monitoring procedure should be in place as mentioned above for early detection of adverse events. (see Detection above)

4. Are procedures in place for handling new risks identified during the study (including treatment of patient, changing trial condition, suspending trial/vaccine lot, investigating and communicating results of investigations, amending investigator’s brochure and consent form etc.)
5. Have procedures for waste disposal and disposal of unused product been described?

5) Communication:

1. Has the applicant provide clear timelines and procedures for communicating new risks to investigators, subjects, Regulatory Authority, REC, sponsor and the public (where applicable)?

Regulatory Authority In-house requirements:

1. Need to have procedures in place to deal with protocol violations and other GCP issues.
2. Need to continue to monitor the potential impact of protocol amendments on the safety of study subjects.
3. Consider strategies for communication with the public and other role players on matters relating to HIV/AIDS clinical trials – particularly when new risks of public health relevance are identified.
4. Need to monitor for concerning trends in SAE reports for HIV/AIDs clinical trials.
ATTACHMENT 3
GUIDELINES PERTAINING TO ADVERSE DRUG REACTIONS REPORTING

A. DEFINITIONS AND TERMINOLOGY

1. ADVERSE DRUG REACTION
2. ADVERSE EVENT
3. SERIOUS ADVERSE DRUG EVENT OR ADVERSE DRUG REACTION
4. UNEXPECTED ADVERSE DRUG REACTION
5. HEALTH CARE PROFESSIONAL
6. ADVERSE DRUG REACTION REPORT
7. SPONTANEOUS REPORT
8. REPORTABLE ADVERSE REACTION – MINIMUM INFORMATION
9. PERIODIC SAFETY UPDATE REPORTS
10. LINE LISTINGS

B. PROCEDURES FOR REPORTING

1. GENERAL PRINCIPLES
   1.1 Who to report to
   1.2 Route of notification
   1.3 Follow-up reports
   1.4 Internal safety monitoring system
   1.5 Report format and details
   1.6 Overdose
   1.7 Teratogenicity and congenital anomalies
   1.8 Product defects
   1.9 Drug Interactions
   1.10 Another applicant’s product
   1.11 Confidentiality
   1.12 Lack of efficacy

2. POST-REGISTRATION ADVERSE REACTION REPORTS
   2.1 Reactions Occurring Locally
   2.2 Reactions Occurring Internationally
   2.3 Periodic Safety Update Reports
   2.4 Case Reports from Published Scientific Literature
   2.5 Reports from Post-registration Studies
   2.6 Ongoing Safety monitoring Evaluation
   2.7 Consumer Reports
   2.8 Reports Relating to Pregnancy and Breast-feeding

3. PRE-REGISTRATION ADVERSE REACTION/EVENT REPORTS
   3.1 Adverse Drug Reaction Reporting for Clinical Trials
   3.2 Other Observations
   3.3 Managing Blinded Therapy Cases
3.4 Medicines Used under Section 21, not within a clinical trial
3.5 Protocol Design Details

C. REFERENCES
D. APPENDICES

Appendix 1: Addresses
Appendix 2: Tabulated Summary of Reporting Requirements
Appendix 3: Report form for suspected adverse drug reactions
Appendix 4: Report form Serious Adverse Events/Reactions (SAEs)
Guidelines Pertaining to Adverse Drug Reaction Reporting

TO ALL APPLICANTS

These guidelines are intended to assist applicants in the reporting of adverse drug reactions (ADRs) associated with medicines and in the management of safety data, which arise during clinical trials.

For the purposes of these guidelines, “Authority” refers to the National Drug Regulatory Authority.

A. DEFINITIONS AND TERMINOLOGY

1. ADVERSE EVENT

“Adverse event/experience” is any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment.

An adverse event can be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

2. ADVERSE DRUG REACTION (ADR) or ADVERSE REACTION

“Adverse drug reaction” or “adverse reaction” means a response to a medicine in humans or animals, which is noxious and unintended, including lack of efficacy, and which occurs at any dosage and can also result from overdose, misuse or abuse of a medicine.

The definition of an adverse drug reaction or adverse reaction applies to registered medicines, medicines for which the applicant holds an application for registration, as well as unregistered medicines being used to treat individual patients. This definition includes any significant hazards to patients.

A reaction, contrary to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected, i.e. judged possible by the reporter or a reviewing health care professional. By virtue of the fact that the health care professional is making a report to an applicant, he/she is indicating that the observed event may be caused by the medicine. All spontaneous reports are therefore suspected adverse drug reactions.

In the case of pre- and post-marketing studies adverse “events” are usually systematically solicited. In cases where there is uncertainty as to whether or not an event is a reaction, it is better to treat the event as a reaction. For the purpose of clinical trials, an adverse drug reaction includes any adverse event where the contribution of the study medication, concomitant medication or other medicinal intervention of the clinical trial cannot be ruled out.
### 3. SERIOUS ADVERSE DRUG EVENT OR ADVERSE DRUG REACTION

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires patient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical and scientific judgement should be exercised in deciding whether other situations are serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples include blood dyscrasias or convulsions not resulting in hospitalisation, or development of drug dependency or drug abuse.

In the case of medicines used in animals, a serious adverse event/reaction includes any such event which may occur in even a single animal within a herd or flock of animals.

### 4. UNEXPECTED ADVERSE REACTION

An “unexpected” adverse reaction is an adverse reaction, the nature, specificity, severity and outcome of which is not consistent with the applicable product information (i.e. the approved package inserts for registered medicines, or the investigator’s brochure or other product information for unregistered medicines being used to treat individual patients.)
5. HEALTH CARE PROFESSIONAL

For the purposes of reporting suspected adverse reactions “health care professional” includes medical practitioners, pathologists, dentists, veterinarians, paraveterinary professionals including veterinary nurses and animal health technicians, pharmacists and nurses.

When reports originate from pharmacists or nurses, further information about the case should, where possible, be sought from a medical practitioner responsible for the patient. Furthermore, if there is more than one reporter, the health care professional directly involved in the patient’s care who provides the most complete and clinically relevant information will be considered the primary reporter.

6. ADVERSE DRUG REACTION REPORT

An adverse drug reaction report is a detailed record of all relevant data associated with the use of a medicine in a subject or patient.

7. SPONTANEOUS REPORT OR SPONTANEOUS NOTIFICATION

A spontaneous report is a communication to a company, regulatory authority or other organisation that describes a suspected adverse drug reaction in a patient given one or more medicines and which does not derive from a study.

8. REPORTABLE ADVERSE REACTION – MINIMUM INFORMATION

A reportable ADR requires the following minimum information:

- An identifiable source (reporter) of the information.
  
  This should include the name or initials and address of the reporter and the reporter’s qualification (e.g. doctor, dentist, pharmacist, nurse or veterinarian).

- An identifiable patient.
  
  A patient may be identified by surname and forename(s) or initials of surname and forenames, or by a reference number. For Veterinary Medicines an identifiable patient requires a description of the animal (particularly species)

- Suspected product(s).

- Suspected reaction(s).
Information, additional to the minimum, should be actively sought and submitted as soon as it becomes available.

9. PERIODIC SAFETY UPDATE REPORTS

A periodic safety update report (PSUR) is an update of the world-wide safety experience of a medicine at defined times post-registration, determined by the international birth date. Each safety update report should cover the period of time since the last update report. The PSUR should be compiled in accordance with the requirements of the ICH E2C (CPMP/ICH/288/95) Expert Group on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.

10. LINE LISTINGS

A line listing provides key information but not necessarily all the details customarily collected on individual cases. Reactions are classified by body system for the most serious presenting sign or symptom. The headings usually included are:

- Country
- Source (physician, literature, etc.)
- Age
- Sex
- Dose of drug
- Duration of treatment (prior to event); time to onset
- Description of reaction (as reported)
- Patient outcome (e.g. fatal, resolved, etc.)
- Comment
- Company Reference Number

In some instances, depending on the type or source, ADR reports should be presented as line listings. A line listing serves to help the Authority to identify cases which it might wish to examine more completely by requesting full case reports.

B. PROCEDURES FOR REPORTING

1. GENERAL PRINCIPLES

1.1 Who to report to:

All reports required by these guidelines should be sent to the Authority at the addresses reflected in Appendix 1.

1.2 Route of Notification:

Reports may be sent by post, facsimile or electronically.
1.3 Follow-up reports:

After initial receipt of an adverse reaction report, a notice of acknowledgement will be sent to the applicant quoting the number assigned to the case report. Any follow-up correspondence from the applicant, relating to the same case report, should be cross-referenced to the assigned database number or to an appropriate unique number assigned by the applicant (relating specifically to the initial notification). This is the only reliable way to minimise the duplication of reports submitted by applicants.

1.4 Internal safety monitoring system:

(i) The applicant should ensure that it has an appropriate system for safety monitoring in place in order to assure responsibility for the management of safety data for its medicines and to ensure that appropriate action can be taken when necessary. It is strongly recommended that the applicant has permanently and continuously at its disposal locally, a qualified person/s responsible for safety monitoring, both for pre- and post-marketing surveillance. This person/s should have experience and training in all aspects of safety monitoring and if not a health care professional, should have access to a medically qualified person.

(ii) The managing director of a pharmaceutical company must nominate a specific individual/s responsible for safety monitoring activities. The Authority must be informed in writing who the responsible person/s is for all matters pertaining to safety monitoring, including the contact details (postal and e-mail addresses and telephone and fax numbers) for such a person/s.

(iii) Responsibilities of the applicant’s safety monitoring officer should include:

- The establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the company or organisation, including to medical representatives and clinical research associates, is collected and collated so that it is accessible at a single point.
- Serving as a contact person for the Authority for any matters relating to safety monitoring.
- The preparation of the following for submission to the Authority:
  - all adverse drug reaction reports
  - Periodic Safety Update Reports (PSURs), when necessary
  - company-sponsored pre- and post-registration study reports
  - ongoing safety monitoring evaluation during the post-registration period.
- Ensuring that any request from the Authority for additional information necessary for the evaluation of the risk-benefit balance of a medicine is reported to the Authority promptly and fully.
1.5 Report Format and Details:

(i) **Post-registration:** Reporting can be done using the adverse reaction report form available from the Authority (appendix 3), or applicants may use their in-house report forms, provided all the necessary data elements are included on the form in a readable format.

(ii) **Pre-registration:** A Serious Adverse Event/Reaction (SAE) reporting form (appendix 4) should be used for reporting of pre-registration clinical trial adverse event/reaction reports. Applicants may use their in-house Adverse Event report forms to submit such reports, provided all the data elements are included on the form in a clearly readable format.

(iii) Applicants should submit **ALL** the relevant information available at the time of initial notification of an adverse drug reaction report i.e. not only the minimum information required for a report. The attachment of discharge summaries, post-mortem reports, relevant laboratory data, and other additional clinical data is encouraged.

(iv) The original words/description (verbatim) used by the initial reporter to describe the adverse reaction should be provided. The medicine/trade name must be provided as reported by the initial reporter.

(v) Additional information, not available at the time of the initial report, should be provided in the form of follow-up reports.

(vi) The applicant is required to submit the name or initials, address and telephone number and qualification of the initial reporter on the adverse drug reaction case report form. In the case of a report from a clinical trial, the trial site at which the reaction occurred needs to be submitted in addition to other information requested.

1.6 Overdose:

Reports of overdose should be submitted only when the overdose was associated with an adverse reaction. Suspected adverse reactions associated with an overdose should be reported as are other reactions. This should include reports that indicate that taking of the suspect medicine led to suicidal intention and subsequent overdose of the suspect medicine or other medication.

1.7 Teratogenicity and congenital anomalies:

For reports on congenital anomalies or teratogenicity:
- Give age and sex of the infant.
- Follow-up reports for the infant should be considered a follow-up to the initial report.
- The birth date or the date pregnancy was terminated should be the event onset date.
- Include date and/or duration of *in utero* exposure where possible.
- Any adverse reaction experienced by the mother must be considered a new initial case report on a separate report form.
1.8 **Product defects:**

If an adverse event is suspected to be related to a product defect, it should be reported in the same manner as a suspected adverse reaction. The lot number of the suspected medicine should be included in the report. Applicants should inform whether the implicated products have been tested for product quality and what (if any) corrective actions are being/have been taken.

1.9 **Drug Interactions:**

Any drug interaction which results in an adverse reaction should be reported as an adverse reaction in the prescribed manner.

1.10 **Another Applicant’s Product:**

(i) **Spontaneous reports:** If a pharmaceutical company receives a report of a suspected adverse reaction to a medicine marketed by another applicant, such a report should promptly be forwarded to the applicant for the medicine. Such reports should not be reported to the Authority by the applicant to whom the event was originally reported. An applicant who receives such a report about its medicine from another applicant is required to submit the report to the Authority with time constraints applicable to any other report.

(ii) **Clinical trials:** When serious, unexpected reactions are found for another applicant’s medicine, used concomitantly during the conduct of a clinical trial, reports should be submitted directly to the Authority by the applicant conducting the study.

1.11 **Confidentiality:**

Strict confidentiality will be maintained by the Authority regarding the identities of the patient and the reporter. Other details relating to the adverse drug reactions, however, are in the public domain.

1.12 **Lack of Efficacy reports:**

“Lack of efficacy” is defined as a failure to produce the expected pharmacological action. Lack of efficacy applies to registered medicines. The lot number of the suspected medicine should be included in the report. If the report of “lack of efficacy” is for an unapproved indication, the event is still reportable.

2. **POST-REGISTRATION ADVERSE DRUG REACTION REPORTS**

2.1 **Reactions occurring in Locally:**

(i) Applicants must report all serious, suspected adverse drug reactions occurring in the country with any medicine, as soon as possible, within 15 calendar days after first knowledge by the applicant.

(ii) Applicants must report all non-serious, unexpected, suspected adverse drug reactions occurring in the country with any medicine, within 15 calendar days after first knowledge by the applicant. Do not report non-serious, expected adverse reactions.
2.2 Reactions occurring Internationally:

(i) Foreign individual case reports should not be forwarded to the Authority on a routine basis, but should be reported in the context of a specific safety issue or on specific request by the Authority.

(ii) The Authority should be advised of any action relating to safety which has been taken by a foreign agency, including the basis for such action, within 3 days of first knowledge by the applicant.

(iii) These guidelines [i.e. 2.2.(i) and (ii)] also apply to medicines for which the applicant holds an application for registration.

2.3 Periodic Safety Update Reports:

(i) PSURs should only be submitted in the following situations:
   a. Whenever requested by the Authority.
   b. When the submission of PSURs is a condition of registration for a new medicinal product or range of medicinal products. These PSURs must be submitted within 30 calendar days of initial receipt by the applicant from the parent company.
   c. As part of a submission for a package insert amendment when the PSUR contains information supporting the amendment.
   d. When a new medicinal product is submitted to the Authority for registration and where the product has already been marketed elsewhere, PSURs should be sent to the Authority during the evaluation period prior to registration. These PSURs must be submitted within 30 calendar days of initial receipt by the applicant from the parent company.
   e. When a clinical trial is being carried out with a product which is already registered in other countries.

(ii) The applicant should inform the Authority of any steps which are taken/to be taken with regard to safety concerns raised in the periodic safety update report at the time of the submission.

(iii) PSURs for unregistered medicines or medicines for which no submission for registration has been made must not be submitted routinely.

2.4 Case reports from published scientific literature:

(i) Applicants should report published suspected adverse drug reactions related to the active substance(s) of their medicinal products, as relevant to the categories identified in 2.1 and 2.2 above. A copy of the relevant published article should be provided.

(ii) An adverse drug reaction report should be completed for each identifiable patient (with an identifiable adverse drug reaction). For instance, if an article describes 6 identifiable patients with a given adverse experience, 6 adverse drug reaction reports should be submitted to the Authority.

(iii) If more than one medicine is mentioned in the literature report, only the applicant whose medicine is suspect of being causative is required to
submit a report. The suspect medicine is usually that mentioned as such by the author or stated in the article's title.

2.5 Reports from post-registration studies:

(i) All suspected adverse reactions from post-registration studies must be reported according to 2.1 above. This applies to reports from any type of clinical or epidemiological investigation involving a medicinal product, independent of design or purpose.

(ii) Investigators involved in post-registration studies should be aware of the definition of what constitutes a serious adverse drug reaction as well as the distinction between ‘reactions’ and ‘events’.

(iii) In the case of post-registration studies adverse “events” are usually systematically solicited. In cases where there is uncertainty as to whether or not an event is a reaction, the case should be reported as an adverse reaction. Events that are clearly unrelated to the medicine should not be reported.

(iv) If the manufacturer receives a report of a serious adverse drug reaction from the investigator who is blinded to individual patient treatment, the guidelines outlined in section 3.3 below should be adhered to.

2.6 On-going Safety monitoring evaluation:

(i) Applicants must inform the Authority within 3 calendar days of first knowledge by the applicant, whenever new evidence becomes available (nationally and internationally) which could significantly impact on the benefit/risk assessment of a medicine or which would be sufficient to consider changes in the conditions of registration of the medicine.

(ii) Applicants must report any change in the nature, severity or frequency of expected adverse drug reactions or any new risk factors identified within 15 calendar days. The basis on which these assessments are made should be included.

(iii) Additional safety monitoring data such as actual case reports, drug usage figures, the regulatory status of the product in other countries, independent pharmacoepidemiology studies, pre-clinical studies or significant product quality data may be requested by the Authority as the situation warrants. This will be requested for submission within a time period specified by the Authority.

2.7 Consumer Reports:

If an applicant receives an adverse drug reaction report from a consumer, the applicant is encouraged to advise the consumer to report this reaction through his/her medical practitioner, pharmacist, nurse, dentist or veterinarian. If this approach fails, the applicant should attempt to obtain as much information as possible from the consumer. However, if the minimum information for reporting has been met, and the report is deemed to be relevant by a health care professional within the company, the case is considered reportable.
2.8 **Reports Relating to Pregnancy and Breast-Feeding:**

The applicant must report suspected adverse drug reactions related to pregnancy or breast-feeding as specified in 2.1 and 2.2 above, regardless of whether or not the drug is contraindicated in pregnancy and/or breast-feeding. Reports on pregnancy should not be forwarded before the outcome is known unless unintended pregnancy is suspected as an adverse drug reaction. Reports on pregnancy should not be submitted if there is no adverse effect to the foetus/infant.

3. **PRE-REGISTRATION ADVERSE DRUG REACTION / EVENT REPORTS**

This applies to reports from any type of clinical or epidemiological trial, independent of design or purpose.

3.1 **Adverse Drug Reaction reporting for Clinical Trials:**

(i) *All fatal and life-threatening, unexpected* adverse drug reactions occurring in clinical trials should be reported within 7 calendar days after first knowledge by the applicant followed by as complete a report as possible within an additional 8 calendar days of the initial information. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicines.

(ii) *Serious, unexpected adverse drug reactions that are not fatal or life-threatening* occurring in clinical trials must be reported as soon as possible but no later than 15 calendar days after first knowledge by the applicant.

(iii) All suspected *serious, unexpected* adverse drug reaction reports originating from world-wide clinical sites *outside the country* for clinical trials conducted with the same medicine should be reported as part of the 6-monthly progress reports in a line listing format.

(iv) The Authority must be notified within 15 calendar days after first knowledge by the applicant when there is a suggestion of a change in the nature, severity or frequency of *expected* adverse drug reactions or when new risk factors are identified. The basis on which these assessments are made should be included.

(v) Any information, which may in any way influence the benefit-risk assessment of a medicine or which would be sufficient to consider changes in the administration of the medicine or in the overall *conduct of a clinical trial*, must be reported to the Authority. This must be submitted to the Authority within 3 calendar days of first knowledge by the applicant. This could include individual case reports or a major safety finding from other sources.

(vi) All serious adverse *events* must be included as part of the 6-monthly progress reports in a line listing format only.

(vii) All non-serious unexpected suspected adverse drug reactions must be included as part of the 6-monthly progress reports in a line listing format only.
(viii) All reports originating locally must be signed by a clinical investigator that has been approved by the Authority as such. A single copy of the original report should be submitted to the Authority.

(ix) If the sponsor of a clinical trial or the applicant for the trial does not agree with the causal association assigned by the initial reporter or the investigator, the reaction should still be reported.

(x) Expedited (rapid) reporting will be inappropriate for serious events from clinical trials that are considered not related to the study product. All cases judged by the clinical investigator or the sponsor as having a reasonable suspected causal relationship to the medicine qualify as adverse drug reactions. (Refer point A.2.)

3.2 Managing Blinded Therapy Cases:

(i) When a serious, unexpected, suspected adverse drug reaction occurs which results in death or is life-threatening, and is therefore judged reportable on an expedited (rapid) basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study’s conclusion.

(ii) When a fatal or other serious outcome is the primary efficacy endpoint in a clinical trial, the integrity of the clinical trial may be compromised if the blind is broken. Under these and similar circumstances, agreement should be reached in advance with the Authority concerning serious events that would be treated as disease-related and not subject to routine expedited (rapid) reporting. An independent data safety monitoring board should be established prior to commencement of the trial and its composition and terms of reference should be submitted with the clinical trial application documents to the Authority for evaluation.

3.3 Post-study events:

Serious adverse events that occur after the patient has completed a clinical trial (including any post-treatment follow-up required according to the protocol) should be regarded for expedited (rapid) reporting purposes as though they were study reports. A causality assessment and determination of expectedness are needed for a decision on whether or not expedited (rapid) reporting is required.

3.4 Unregistered Medicines used to treat individual patient, not within a clinical trial

The prescriber of a medicine approved for use by the Regulatory Authority for patients not enrolled in a clinical trial (e.g. compassionate use, named-patient use), must report any serious suspected adverse drug reaction occurring with the use of the medicine in the specified patient/s within 15 calendar days of first knowledge by the prescriber.

3.5 Protocol design details:

(i) Each clinical trial protocol submitted to the Authority, should include a risk management procedure, including unblinding procedures, for dealing
with serious, unexpected events or reactions which may arise during the conduct of the trial and which could significantly impact on the safety of the study subjects.

(ii) There may be differences in the clinical safety profile for different presentations, e.g. dosage form, formulation or delivery system, of the pharmacologically active compound(s) or different indications/uses of a given product. All adverse reactions which qualify for reporting should be cross-referenced for all other dosage forms and uses for that product. The Investigator’s Brochure must therefore cover adverse drug reaction information that applies to all product presentations and uses.
C. REFERENCES


ADRguid6.rtf
D. APPENDICES

APPENDIX 1: TABULATED SUMMARY OF REPORTING REQUIREMENTS

Post-Registration ADR Reports (registered medicinal products)

<table>
<thead>
<tr>
<th>Type of ADR report</th>
<th>Time frame for reporting</th>
<th>A. Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Reports (spontaneous/published/study):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious (expected and unexpected)</td>
<td>15 days</td>
<td>ADR form #</td>
</tr>
<tr>
<td>Non serious (unexpected)</td>
<td>15 days</td>
<td>ADR form #</td>
</tr>
<tr>
<td>Non serious (expected)</td>
<td>No report</td>
<td>Not required</td>
</tr>
<tr>
<td>Foreign Reports (spontaneous/published/ study):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>On request or relating to specific safety issue</td>
<td>As appropriate</td>
</tr>
<tr>
<td>Notification of Change in Nature, Severity or Frequency or Risk factors</td>
<td>15 days</td>
<td>Detailed report (including publications)</td>
</tr>
<tr>
<td>New information impacting on benefit-risk profile of product including international regulatory decisions</td>
<td>3 days</td>
<td>Detailed report (including publications)</td>
</tr>
</tbody>
</table>

# Applicant’s in-house ADR report form or Regulatory Authority ADR report form.

Pre-Registration ADR/ADE reports (i.e. unregistered medicines)

<table>
<thead>
<tr>
<th>B. Type of ADR report</th>
<th>Time frame for reporting</th>
<th>C. Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Reports:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal or life-threatening (unexpected)</td>
<td>7+8**</td>
<td>SAE form</td>
</tr>
<tr>
<td>Other serious (unexpected)</td>
<td>15 days</td>
<td>SAE form</td>
</tr>
<tr>
<td>All (local &amp; foreign) reports:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious (unexpected and expected) events</td>
<td>6 monthly##</td>
<td>Line listing</td>
</tr>
<tr>
<td>Non-serious unexpected reactions</td>
<td>6 monthly</td>
<td>Line listing</td>
</tr>
<tr>
<td>Notification of Change in Nature, Severity or Frequency or Risk factors</td>
<td>15 days and in 6 monthly report##</td>
<td>Detailed report</td>
</tr>
<tr>
<td>New information impacting on risk-benefit profile of product or conduct of trial</td>
<td>3 days and in 6 monthly report##</td>
<td>Detailed report</td>
</tr>
</tbody>
</table>

## 6-monthly progress report which should be submitted to the Authority during the entire duration of the clinical investigation.

** 7+8 - initial notification to the Authority as soon as possible but within 7 calendar days followed by a complete report within 8 calendar days of the initial notification.