



SAHPRA

South African Health Products Regulatory Authority

APPLICATION TO CONDUCT A CLINICAL TRIAL

| | |
|--|--|
| Study title | |
| Protocol No. | |
| Version No. | |
| Study Medicine | |
| SAHPRA* Ref. no. (if applicable) | |
| SAHPRA* Ref number(s) of comparator medicine(s) (if applicable) | |
| SAHPRA* Ref number(s) of concomitant medicine(s) (if applicable) | |
| Date(s) SAHPRA approval or previous protocol(s) | |
| Sponsor: | |
| Applicant: | |
| Contact Person: | |
| Address: | |
| Telephone No.: | |
| Fax No.: | |
| Cell No.: | |
| E-mail address: | |
| Date of Application: | |

*Refers to registration number for registered medicines issued by MCC

Check-list

Refer to the Appendix for instructions

| | |
|--------------------------|---|
| <input type="checkbox"/> | Cover Letter |
| <input type="checkbox"/> | Cover page and fully completed application |
| <input type="checkbox"/> | Two additional completed signed copies of the clinical trial application |
| <input type="checkbox"/> | Protocol |
| <input type="checkbox"/> | Patient Information Leaflet(s) AND Informed Consent Form(s) |
| <input type="checkbox"/> | Copy/ies of Recruitment Advertisement(s) (if applicable) and Questionnaires |
| <input type="checkbox"/> | Investigators' Brochure and / or all Professional Information (Package Insert(s)) |
| <input type="checkbox"/> | Certificate(s) of Analysis |
| <input type="checkbox"/> | Signed Investigator's CV(s) in SAHPRA format |
| <input type="checkbox"/> | Signed Declaration(s) by all Investigator(s) |
| <input type="checkbox"/> | Signed Joint Financial Declaration (Sponsor and National PI) |
| <input type="checkbox"/> | Signed Declaration by Applicant and National Principal Investigator |
| <input type="checkbox"/> | CV(s) and Signed Declaration by Regional Monitor(s) |
| <input type="checkbox"/> | Proof of Application to Register the Trial on the South African National Clinical Trials Register |
| <input type="checkbox"/> | Active Insurance Certificate for Clinical Trial |
| <input type="checkbox"/> | Proof of Sponsor Indemnification for Investigators and Trial Site |
| <input type="checkbox"/> | GCP Certificates |
| <input type="checkbox"/> | Workload Forms for Investigators |
| <input type="checkbox"/> | Proof of Registration with Professional Statutory Body (HPCSA, SAPC, SANC, etc) |
| <input type="checkbox"/> | Proof of Professional Indemnity (Malpractice Insurance) |
| <input type="checkbox"/> | Ethics Approval Letter or Copy of letter submitted to Ethics Committee |
| <input type="checkbox"/> | Study Budget |
| <input type="checkbox"/> | Citations |
| <input type="checkbox"/> | Two Labelled CD-ROM (List of files submitted on CD-ROM) |
| <input type="checkbox"/> | Proof of payment |

NB: Incomplete documentation or sub-standard submissions will be rejected.

Applications submitted without Clinical Trial Insurance will be rejected.

Application should be ring-bound. Lever arch files will not be accepted.

Declaration by Applicant

I/We, the undersigned have submitted all requested and required documentation, and have disclosed all information which may influence the approval of this application.

I/We, the undersigned will ensure that if the above-said clinical trial is approved, it will be conducted according to the submitted protocol and South African legal, ethical and regulatory requirements.

1st Applicant (local contact)

Date

Alternative (local contact)

Date

Declaration by National Principal Investigator

I, the undersigned as National Principal Investigator agree that I have reviewed the application and protocol and will ensure that if the above-said clinical trial is approved, it will be conducted according to the submitted protocol and South African legal, ethical and regulatory requirements.

National Principal Investigator /
Other (state designation)

Date

SECTION 1: ADMINISTRATIVE

| PART 1: ADMINISTRATIVE DETAILS | |
|--|--|
| 1.1 Study Title | |
| 1.2 Protocol No, Date and Version | |
| 1.3 Phase of trial | |
| 1.4 Sponsor | |
| 1.5 Applicant | |
| 1.6 Contact Person (Address, Telephone Number, Fax Number, E-mail Address) | |
| 1.7 National Principal Investigator/ Coordinator (or equivalent person) | |
| 1.8 International Principal Investigator (if applicable) | |
| 1.9 Regional Monitor | |

| PART 2: DETAILS OF TRIALISTS AND SITES | |
|---|--|
| 2.1 Details of Site(s) (Name of site, physical address, contact details, contact person) | |
| 2.2 Details of how sites were selected | |
| 2.3 Details of investigators and staff (Investigators, staff, number of staff, names, qualifications, experience) | |
| 2.4 Details of capacity of site(s): (site facilities, equipment, emergency facilities, other relevant infrastructure and investigator work load documents) | |
| 2.5 Details and evidence of competence of the laboratories: <ul style="list-style-type: none"> • Collection and processing of samples for shipping to centralised testing facilities (include conditions of shipping) • Bedside/point-of-contact testing and details of training of staff • Screening and safety testing of clinical samples during the trial • Specialised end-point testing (virology, immunology, cytokine analysis) | |

| PART 3: REGULATORY DETAILS | |
|---|--|
| 3.1 Name other Regulatory Authorities/ Ethics Committees to which application to do this trial have been submitted, and/or approved | |
| 3.2 If the trial is to be conducted in SA and not in the host country of the applicant / sponsor, provide an explanation | |
| 3.3 Name other Regulatory Authorities or Ethics Committees which have rejected this trial and give reasons for rejection | |
| 3.4 If applicable, details of and reasons for this trial having been halted at any stage by other Regulatory Authorities | |

SECTION 2: CLINICAL TRIAL PROTOCOL

| PART 4: INVESTIGATIONAL PRODUCT (IP) AND OTHER MEDICINES | |
|---|--|
| 4.1 | Details of IP (name, strength, formulation, dose(s), mode of administration and other relevant IP details) |
| 4.2 | Properties of IP i.e. mechanism of action |
| 4.3 | Summary of Pre-clinical findings (e.g. laboratory / animal / toxicity / mutagenicity) |
| 4.4 | Summary of Clinical Findings (e.g. phases; PK; PD; dose-finding; ADRs, NNT/NNH, other). |
| 4.5 | Details of comparator medicine(s) (name strength, formulation, dose(s), mode of administration and justification of the choice of the comparator) |
| 4.6 | Name(s) and details (as above) of concomitant medication(s) including rescue medications which are required or excluded in the protocol |
| 4.7 | Registration status of IP, concomitant and/or comparator medicine(s) (include Investigator's brochure, SAHPRA approved PI, and other international professional information (package inserts) if not approved in SA and certificate of analysis) |
| 4.8 | Estimated Quantity of Trial Material (each medicine detailed separately) for which exemption will be required (including overage and justification for overage if above 20 %) |
| 4.9 | If any of the above medicines are available in South Africa, give an explanation why they need to be imported from elsewhere |
| 4.10 | Details of medicine(s) supply management and accountability (receipt of medicine(s) from supplier, storage, dispensing, packaging and labelling of Investigational Product) |
| 4.11 | Give details of intention to register and justify if registration is not envisaged |
| 4.12 | Details of the manufacture, quality control and stability of the IP |
| 4.13 | Previous studies using this medicine which have been approved by SAHPRA* and include SAHPRA* approval number Study title, Protocol number, Date of approval, National PI / Principal Investigator, Date(s) Progress report(s) and Date Final report) |

**This means all studies approved in the previous Medicines Control Council dispensation*

| PART 5: BACKGROUND INFORMATION | |
|--|--|
| 5.1 Disease / problem in South African context (e.g. local epidemiology) | |
| 5.2 Overall rationale for the study summarised | |
| 5.3 Rationale for the study in the South African context | |

| PART 6: STUDY OBJECTIVES AND ENDPOINTS (with justifications) | |
|---|--|
| 6.1 Primary objectives and endpoints | |
| 6.2 Secondary objectives and endpoints | |
| 6.3 Exploratory objectives and endpoints | |
| 6.4 Safety objectives and endpoints | |
| 6.5 Other objectives | |

| PART 7: STUDY DESIGN AND METHODOLOGY | |
|---|--|
| 7.1 Study Design (with justifications) <ul style="list-style-type: none"> • phase of trial • choice of design • use of placebo (if applicable) • dosages • randomisation • blinding | |
| 7.2 Duration of the study | |
| 7.3 Planned start and stop date of the study | |
| 7.4 Participant numbers (local and worldwide) include participant numbers per site in South Africa | |
| 7.5 Provide information indicating potential of each site to recruit required number of patients within envisaged duration of trial | |
| 7.6 Provide details of pharmacogenetic, biobanking or other sub-studies planned | |

| PART 8: ELIGIBILITY CRITERIA (with justification for each criterion) | |
|---|--|
| 8.1 Inclusion criteria | |
| 8.2 Exclusion criteria | |

| PART 9: DATA AND SAFETY MONITORING PLAN | |
|---|--|
| 9.1 Describe and comment on Data and Safety monitoring plan (provide detailed safety and monitoring plan for the study and explain how adequate site oversight will be ensured) | |
| 9.2 Provide details of Composition, Charter and Stopping rules of the Data Safety Monitoring Committee if applicable | |
| 9.3 Provide details of interim analyses if planned | |
| 9.4 Provide AE and SAEs definitions, reporting guidelines and causality assessments to be followed Provide details of AE's and SAEs of special interest | |

| PART 10: STATISTICAL MEASURES | |
|---|--|
| 10.1 Provide method of Sample size determination (justification of the power of the study in relation to the outcomes measures) | |
| 10.2 Provide Statistical method(s) and analysis of qualitative and/or quantitative measures with appropriate, clear justification | |
| 10.3 Details of data processing <ul style="list-style-type: none"> • how • where • when • who | |

| PART 11: ETHICAL AND ADMINISTRATIVE ISSUES | |
|--|--|
| 11.1 Justification for deviation from current SA GCP guidelines | |
| 11.2 Provide details of capacity building and transformation at all sites | |
| 11.3 Provide details of insurance (including title, protocol, dates, policy #, amount, local vendor) | |
| 11.4 Provide details of indemnity for Investigators and trial site | |

| PART 11: ETHICAL AND ADMINISTRATIVE ISSUES | |
|---|--|
| 11.5 Ensure Patient Information Leaflet and Informed Consent / Assent includes: <ul style="list-style-type: none"> • latest ABPI and SA GCP guidelines • written in appropriate level of education /English • explains possible benefits / risks • ensuring patient rights • SAHPRA and Ethics contact names and numbers • Other details as per ICH GCP • Confirm translations available | |
| 11.6 Provide separate PILs and informed consent forms for any proposed <ul style="list-style-type: none"> • archiving of blood specimens for later research • genetics research • HIV testing • any other | |
| 11.7 Provide details of publication policy | |
| 11.8 Provide details of remuneration and other benefits for participants | |
| 11.9 Provide details of remuneration of investigators or site | |
| 11.10 Provide a list of Ethics Committees which will be involved in approving the study | |
| 11.11 Provide details of possible conflict of interest of any person(s)/ organisation(s) who/which will be involved in the trial | |
| 11.12 Provide updated proof of GCP training for staff involved in this trial (done in the past three years) | |
| 11.13 Provide details on treatment and/or management of participants and their disease condition(s) after completion of trial (Post trial medicine access) | |

| PART 12: ADDITIONAL COMMENTS | |
|--|--|
| Provide any additional information that may be relevant to the study | |

Annexure 1

STANDARDISED WORDING TO BE ADDED TO PATIENT INFORMATION LEAFLET (PILs)

If you have questions about this trial, you should first discuss them with your doctor or the Ethics Committee (contact details as provided on this form). After you have consulted your doctor or the Ethics Committee and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

The Chief Executive Officer

South African Health Products Regulatory Authority

Department of Health

Private Bag X828

PRETORIA

0001

E-mail: Portia.Nkambule@health.gov.za

Tel: +27 12 3958126

Annexure 2

| SAHPRA FORMAT FOR CVs OF INDIVIDUALS PARTICIPATING IN THE CONDUCT OF CLINICAL TRIALS IN SOUTH AFRICA | |
|--|-------|
| 1. Trial: | |
| 2. Protocol: | |
| 3. Designation: (e.g. National Principal Investigator, Investigator (Principal, Co- or sub-), Study Co-ordinator, Regional Monitor, Local Monitor, Contract Research Affiliate) | |
| 4. Personal Details | |
| Name: | |
| Work Address: | |
| Telephone Number: | |
| Fax Number: | |
| Cell-phone Number: | |
| e-mail address: | |
| 5. Academic and Professional Qualifications | |
| 6. Professional Statutory body registration number i.e. HPCSA, SAPC, SANC, etc. | |
| 7. Current personal medical malpractice insurance details (all investigators) | |
| 8. Relevant related work experience (brief) and current position | |
| 9. Participation in clinical trials research in the last three years (title, protocol number, designation) [If multiple trials, only list those with relevance to this application, or in the last years.] | |
| 10. Peer-reviewed publications in the past 3 years | |
| 11. Date of last GCP training (as a participant or presenter) | |
| 12. Any additional relevant information supporting abilities to participate in conducting this trial. [briefly] | |
| 13. Signature: | Date: |

Annexure 3

DECLARATION BY CO- AND PRINCIPAL INVESTIGATOR

Name:

Title of Trial:

Protocol:

Site:

1. I have read and understood 'Responsibility of The Principal Investigator (PI) and Participating Investigators' of the current Good Clinical Practice Guidelines of the Department of Health.
2. I have notified the South African Health Products Regulatory Authority (SAHPRA) of any aspects of the above guidelines with which I do not / am unable to, comply. (If applicable, this may be attached to this declaration.)
3. I have thoroughly read, understood, and critically analysed (in terms of the South African context) the protocol and all applicable accompanying documentation, including the investigator's brochure, patient information leaflet(s) and informed consent form(s).
4. I will conduct the trial as specified in the protocol.
5. To the best of my knowledge, I have the potential at the site(s) I am responsible for, to recruit the required number of suitable participants within the stipulated time period.
6. I will not commence with the trial before written authorisations from the relevant ethics committee(s) as well as the SAHPRA have been obtained.
7. I will obtain informed consent from all participants or if they are not legally competent, from their legal representatives.
8. I will ensure that every participant (or other involved persons, such as relatives), shall at all times be treated in a dignified manner and with respect.
9. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.
*[Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.]**
 *Modified from: Davidoff F, *et al.* Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)
10. I have* / have not (delete as applicable) previously been the principal investigator at a site which has been closed due to failure to comply with Good Clinical Practice. (*Attach details.)
11. I have* / have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details)
12. I will submit all required reports within the stipulated time-frames.

Signature:

Date:

Witness:

Date:

Annexure 4

JOINT DECLARATION BY SPONSOR (OR REPRESENTATIVE) AND PRINCIPAL INVESTIGATOR (OR NATIONAL PRINCIPAL INVESTIGATOR) CONCERNING SUFFICIENT FUNDS TO COMPLETE STUDY*

Title:

Protocol:

I, <full name>, representing <sponsor or representative>

And

I, <full name>, Principal Investigator/National Principal Investigator

Hereby declare that sufficient funds have been made available to complete the above-identified study.

Signed:

Date:

SPONSOR (or alternative)

Name:

Address:

Contact details:

Signed:

Date:

PRINCIPAL INVESTIGATOR (or National PI)

Name:

Address:

Contact details:

Annexure 5

| PROVISIONAL DECLARATION BY SUB-INVESTIGATORS AND OTHER STAFF INVOLVED IN A CLINICAL TRIAL | |
|--|-------|
| Name: | |
| Title of Trial: | |
| Protocol: | |
| Principal Investigator's Name: | |
| Site: | |
| Designation: | |
| <ol style="list-style-type: none">1. I will carry out my role in the trial as specified in the protocol.2. I will not commence with my role in the trial before written authorisations from the relevant ethics committee(s) as well as the South African Health Products Regulatory Authority (SAHPRA) have been obtained.3. If applicable to my role in the trial, I will ensure that informed consent has been obtained from all participants or if they are not legally competent, from their legal representatives.4. I will ensure that every participant (or other involved persons, such as relatives), shall at all times be treated in a dignified manner and with respect.5. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial. <i>[Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.]*</i> *Modified from: Davidoff F, <i>et al.</i> Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)6. I have* / have not (<i>delete as applicable</i>) previously been involved in a trial which has been closed due to failure to comply with Good Clinical Practice. (<i>*Attach details</i>)7. I will submit all required reports within the stipulated time-frames. | |
| Signature: | Date: |
| Witness: | Date: |

Annexure 6

| DECLARATION BY REGIONAL MONITOR | |
|--|-------|
| Name: | |
| Title of Trial: | |
| Protocol: | |
| Principal Investigator's Name: | |
| Site: | |
| Designation: | |
| <ol style="list-style-type: none">1. I have read and understood "The Monitor" of the current Clinical Trials Guidelines of the Department of Health.2. I have notified the South African Health Products Regulatory Authority of any aspects of the above guidelines with which I do not / am unable to, comply. <i>(If applicable, this may be attached to this declaration.)</i>3. I will carry out my responsibilities as specified in the trial protocol and according to the current Good Clinical Practice Guidelines of the Department of Health.4. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial. [Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.]* *Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)5. I have* / have not <i>(delete as applicable)</i> previously been the monitor at a site which has been closed due to failure to comply with Good Clinical Practice. <i>(*Attach details.)</i>6. I have* / have not <i>(delete as applicable)</i> previously been involved in a trial which has been closed as a result of unethical practices. <i>(*Attach details)</i>7. I will submit all required reports within the stipulated time-frames. | |
| Signature: | Date: |
| Witness: | Date: |

Annexure 7

WORDING FOR THE SPONSOR INDEMNIFICATION FOR SITES AND INVESTIGATORS

In consideration of the {PI's / Institution's / Research Unit's} participation in the study, we shall indemnify and hold harmless [Name of PI / Institution / Research Unit] and its employees from any legal liability for costs or damages for death or personal injury which may result from the administration of [Name of compound] pursuant to the said study. This indemnity does not apply to the extent that such death or personal injury arises out of any negligent act, default or omission of [Name of PI / Institution / Research Unit] or its employees. Furthermore, this indemnity is subject to the condition that the study is carried out in accordance with the Protocol approved by us in writing, that [Name of Sponsor] is notified immediately on receipt of any claim, that [Name of Sponsor] shall have full control of the management and defence of any such claim and that no offer to compromise or settle any claim is made without the written agreement of [Name of Sponsor].

Note: The wording for Sponsor Indemnification for investigators and sites serves as a guide and is not an exclusive approach.

Annexure 8

| WORKLOAD | | | |
|---|---------------------------------|-------|---|
| Investigator (Name and designation): | | | |
| Total number of current studies (all stages) on specified date | Number | Date | |
| Total number of patients / participants for which responsible on specified date | Number | Date | |
| ESTIMATED TIME PER WEEK [168 hours denominator] | | Hours | % |
| Clinical trials | Clinical work (patient contact) | | |
| | Administrative work | | |
| Organisation (Practice / university / employer) | Clinical work | | |
| | Administrative work | | |
| Teaching | Preparation / evaluation | | |
| | Lectures / tutorials | | |
| Writing up work for publication / presentation | | | |
| Reading / sourcing information (e.g. internet searches) | | | |
| Other (specify) | | | |

UPDATE HISTORY

| Date | Reason for Update | Version & Publication |
|-------------|--|----------------------------------|
| May 2003 | First version published for implementation | Version 1, May 2003 |
| April 2017 | Revised version published for implementation | Version 2, October 2017 |
| May 2018 | Revised version published for implementation | Version 3, June 2018 |

APPENDIX

Requirements for submission of a clinical trial application

Note: This Appendix should not be submitted with the application form

The following are the requirements when submitting a clinical trial application.

1. Cover letter (letter of application)
2. Checklist
3. Two hard copies of complete Clinical Trial Application documents and two Compact Discs (CDs) (see below) with all the required documents (electronic application form must be in MS-WORD version 2007 and above, not PDF and must be signed). The application should be ring-bound and not submitted in lever arch files

CD-ROM Requirements

The following statement should be included in the letter of application, after having confirmed that the submission is virus-free:

"We confirm that the CD burning session is closed and the submission is checked with an up-to-date and state-of-the art virus checker: *[name of the antivirus software and version of the virus checker]* and is virus-free". CD (CD-ROM) conforming to ISO 9660 or ISO 13346 can be accepted.

The use of re-writable disks is not encouraged. When using a re-writable disk, all open sessions must be closed before sending the CD.

The CD should be packed adequately to prevent damage to the media.

Each CD should include the following label information, clearly presented and printed on the media:

- The applicant's name
- The clinical trial applied for
- The submission date (MM-YYYY)

The data on the CD should not be packed into a zip-file, rar-file or any other file format that has been compressed.

One-time security settings or password protection is not acceptable during transportation from the applicant to SAHPRA.

4. Additional 2 completed copies of the clinical trials application form (CTF1)
5. Protocol
6. Patient Information leaflets and Informed consent forms (PIL/ICF). Include a standardised South African Health Products Regulatory Authority (SAHPRA) contact details in PIL/ICON (**Annexure 1**)
7. Relevant questionnaires
8. Investigators Brochure / SAHPRA and other regulatory authorities' approved professional information (Package insert(s))
9. Certificate of analysis of the product
10. Signed investigator(s) Curriculum Vitae(s) (CV) in SAHPRA format (**Annexure 2**)
11. Signed declaration by Co- or Principal investigator(s) (**Annexure 3**)
12. Signed joint declaration by Sponsor/National Principal investigator (**Annexure 4**)
13. Signed declaration by Applicant
14. Signed declaration by National Principal investigator (**See page 4 and Annexure 3**)
15. Signed declaration by Sub-investigators (**Annexure 5**)
16. Curriculum Vitae(s) (CV) and signed declaration by regional monitor (**Annexures 2 and Annexure 6**)
17. Proof of application to register the trial on the South African National Clinical Trials Register

18. Active Insurance Certificate for clinical Trial
19. Proof of Sponsor Indemnity for Investigators and trial site(s) (**Annexure 7**)
20. GCP Certificates (not more than 3 years old)
21. Workload forms for investigators (**Annexure 8**)
22. Proof of registration with professional statutory bodies
23. Proof of professional indemnity (Malpractice insurance) of trialist(s)
24. Ethics Committee(s) approval letter or Copy of letter submitted to Ethics committee(s).
25. Study Budget
26. Citations
27. Proof of payment