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| APPLICATION FOR PROTOCOL AMENDMENT TO APPROVED TRIAL |

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| This document is intended to be used for applying for protocol amendment to approved trial |

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| Publication released for implementation | v2 April 2019 |
| Revised released for implementation | v3 March 2020 |

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| **Study title** |  | |
| Protocol No. |  | |
| Version No. and date\* |  | |
| Study Medicine |  | |
| Sponsor: | |  |
| Applicant: | |  |
| Contact Person: | |  |
| Address: | |  |
| Telephone No.: | |  |
| Fax No.: | |  |
| Cell No.: | |  |
| E-mail address: | |  |
| Date of Application: | |  |

**Check-list**

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| **Cover Letter (describing the extent of amendment and reasons for change)** **one signed in PDF and one in MS-Word format** |
| **Two copies of clinical trial application for amendment (fully completed copies)** **one in PDF and one in MS-Word format** |
| **Original Protocol Synopsis** |
| **Amended Protocol (track changes)** |
| **Amended Protocol (clean copy)** |
| **A Table/succinct summary of all changes to the Protocol** |
| **Certificate(s) of Analysis and comparability data, i.e Change in Investigational formulation and/or excipients, etc.** |
| **Stability Data i.e. for extension of shelf-life** |
| **Revised Patient Information Leaflet(s); Informed Consent Form(s); and/or ASSENT, if applicable** |
| **Good Manufacturing Practice Certificate, if applicable i.e Change in Manufacturer** |
| **Active Insurance Certificate for Clinical Trial Participants, if applicable i.e. increase in number of participants, extension of study, etc** |
| **Revised Investigator’s Brochure and / or all Professional Information / Package Insert(s)), if applicable** |
| **Ethics Approval Letter or Copy of letter submitted to Ethics Committee** |
| **Two Labelled CD-ROM (List of files submitted on CD-ROM)** |
| **One USB flash drive** |
| **Any additional information (list them), if applicable** |
| **Proof of payment** |

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

***Guidance for Amendments application***

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| **MINOR AMENDMENTS** |
| Changes that do not affect safety, design, analysis/results. Examples of minor amendments are listed below and are not limited to the following: |
| **ADMINISTRATIVE** |
| **Change in CRO, Sponsor, Applicant or change of address** |
| **Additional Investigators (CTF 3 submission)** |
| **Additional sites (CTF3 submission)** |
| **Increase in number of local participants** |
| **Increase in number of Investigational Product (IP) to be imported** |
| **Any other Administrative changes (list them)** |
| **CLINICAL** |
| **Change in the background information – Protocol** |
| **Tightening of inclusion criteria** |
| **Tightening of exclusion criteria** |
| **Extension of period of study (e.g low or high recruitment)** |
| **Other changes that do not affect the study or analysis/results** |

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| **MAJOR AMENDMENTS** |
| Changes that affect safety, design, analysis/results. Examples of major amendments are listed below and are not limited to the following: |
| **Change in inclusion criteria** |
| **Change in exclusion criteria** |
| **Change in phase of study** |
| **Change in data analyses** |
| **Change in statistical component (including increase in overall number of participants)** |
| **Change in: dose of IP, route of administration, change in formulation, manufacturer, frequency, excipients, storage conditions, etc** |
| **Change in IP specification or source** |
| **Changes due to new safety data (significant changes may warrant study termination and subsequent submission of new trial)** |
| **Extension of period of study (e.g affect safety, study design/statistical component)** |
| **Any change that impacts on patient safety, quality or the analysis of data (major safety warning requires new application** |

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| **MAJOR AMENDMENTS REQUIRING NEW CLINICAL TRIAL APPLICATION** |
| The changes that require new application. Examples of changes that require a new trial application (CTF-1) are listed below and are not limited to the following: |
| **Change in IP** |
| **Extension of Study i.e rollover studies** |
| **Change in standard of care arm** |
| **Addition or removal of study arm - including comparator or active control of arm (except approved as part of initial study)** |
| **Major safety warning** |
| **Major change in objectives, endpoints and rationale of the study** |
| **Change in study design** |

## SECTION 1: ADMINISTRATIVE

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| **PART 1: ADMINISTRATIVE DETAILS** | |
| 1.1 SAHPRA Reference number |  |
| 1.2 Study Title |  |
| 1.3 Approved Protocol No, Date and Version |  |
| 1.4 Phase of trial |  |
| 1.5 Sponsor |  |
| 1.6 Applicant |  |
| 1.7 Date of approval of original protocol |  |
| 1.8 Details of investigators and sites already approved for this trial (Name of sites, investigators, Designation (whether Principal Investigators or Sub-Investigator). |  |
| 1.9 This Amendment No, Protocol Version No, and date of amendment\*. |  |
| 1.10 Is this amendment local or global? |  |

\*This Amendment No, Protocol version No, and date of amendment- is the one requiring approval for.

In this section provide summary, rationale/justification and risk assessment statement.

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| **PART 2: CHANGES TO THE APPROVED NUMBER OF PARTICIPANTS** | |
| 2.1 Number of trial participants already approved for this trial in South Africa. |  |
| 2.2 Number of trial participants required for this trial globally. |  |
| 2.3 South African context:  Does the applicant wish to increase or reduce the number of participants in this trial?  □ No  □ Yes  If “Yes”, provide details of this increase or decrease, together with a justification/rationale for the change cross-referenced to the amended protocol text. |  |

## SECTION 2: PROTOCOL AMENDMENT

| **PART 3: AMENDMENT DETAILS** | |
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| 3.1 Does the applicant wish to change the eligibility criteria for this trial?  □ No  □ Yes  If “Yes”, provide the tracked changes protocol as well as a justification/rationale for these changes cross-referenced to the amended protocol text. |  |
| 3.2 Does the applicant wish to change the primary and/or secondary objectives of this trial?  □ No  □ Yes  If “Yes”, provide the protocol showing tracked changes of these changed objectives as well as a justification/rationale for the changes (cross-referenced to the amended protocol text). |  |
| 3.3 Does the applicant wish to change the duration of this trial?  □ No  □ Yes  If “Yes”, provide details of the justification/rationale for the changes (cross-referenced to the amended protocol text). |  |
| 3.4 Does the applicant wish to change the dose/regimen/route of administration/frequency of the study drug?  □ No  □ Yes  If “Yes”, provide the protocol with the tracked changes as well as a motivation and scientific justification/rationale for these changes (cross-referenced to the amended protocol text). |  |
| 3.5 Does the applicant wish to add a sub-study for this trial?  □ No  □ Yes  If “Yes”, provide protocol as well as a motivation and scientific justification/rationale for the sub-study. |  |
| 3.6 Is there any other substantial and/or significant change affected by this amendment?  □ No  □ Yes  If “Yes”, provide a summary and the tracked changes to the protocol as well as a justification/ rationale for these changes. |  |
| 3.7 Does the proposed amendment require a new consent for from the participant?  □ No  □ Yes  If “Yes”, submit the new Patient Information Leaflet/Informed Consent Form and /or ASSENT together with this application and summarise the resultant changes. |  |
| 3.8 Do the changes impact on the statistical analysis?  □ No  □ Yes  If “Yes”, provide a summary and justification/rationale thereof. |  |
| 3.9 Are there any other changes affected by this amendment?  □ No  □ Yes  If “Yes”, provide a summary of the tracked changes as well as a motivation and scientific rationale for these changes. |  |

## SECTION 3: ETHICS

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| **PART 4: ETHICS COMMITTEE APPROVAL** | | |
| 4.1 Has/ve the Ethics Committee(s) responsible for each centre to which this amendment applies been notified? | |  |
| 4.2 List the relevant Ethics Committee(s) and date of application. | |  |
| 4.3 Status of Ethics Committee(s) approval of amendment. | |  |
| I, the undersigned, agree to conduct/manage the above-mentioned trial under the conditions as stated in this application | | |
| Applicant:  Signature:…………………………………………………… | Date  ……………………………………. | |

## APPENDIX

**Requirements for submission of amendment application**

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

The following are the requirements when submitting amendment application at SAHPRA reception:

1. Cover letter (letter of application), two hard copies

2. Proof of Payment, two hard copies

3. Two Compact Discs (CDs) containing complete amendment application documents with all the required documents

4. One USB flash drive containing complete amendment application documents with all the required documents

**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 SAHPRA reference number
* The Protocol number and version

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.

**USB flash drive Requirements**

It should be packaged to include the following label information, clearly presented and printed on the packaging:

* The applicant’s name
* The Protocol number
* The submission date (MM-YYYY)

The data on it 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.

**CD and USB flash drive content must contain complete amendment application documents.**