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| **APPLICATION FOR A PROTOCOL AMENDMENT TO AN APPROVED TRIAL** |

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

**Document History**

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| **Final Version** | **Reason for Amendment** | **Effective Date** |
| 2 | New published for implementation | April 2019 |
| 3 | Revised version published for implementation | 3 March 2020 |
| 4 | Administrative Changes for implementation and revisions to sections: Administrative details section, checklist, guidance for amendment applications (Administrative, Clinical & Major amendments) and the appendix section | September 2022 |

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

**CHECKLIST**

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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 (signed) 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** |
| **Any additional information (list them), if applicable** |
| **Proof of payment (Bank verified with an additional itemised allocation statement in case of bulk payment)** |

**NB:**

* **The CTF2 is the primary submission document, please incorporate all changes into the CTF2 and not reference to supportive documents.**
* **Incomplete documentation or poor quality 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 (CTF3 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)** |
| **Minor IMPD amendments e.g. changes to: Manufacturer(s) of drug substance** |
| **CLINICAL (TECHNICAL)** |
| **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 or scope of the investigation** |

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| **MAJOR AMENDMENTS (TECHNICAL)** |
| Changes that affect safety, design, analysis/results. Examples of major amendments are listed below and are not limited to the following: |
| **Change of inclusion/exclusion criteria** |
| **Change in phase of study** |
| **Change in data analyses** |
| **Change in statistical component (Addition or reduction of sample size of the study)** |
| **Change in: dose of IP (including adjustments), route of administration, change in formulation, manufacturer, frequency, excipients, storage conditions,** **Changes in the manufacturing process and/or specifications of an active substance /IMP 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)** |
| **Changes that result in the extension of duration of a trial (e.g affect safety, study design/statistical component)** |
| **Major IMPD quality changes include but are not limited to changes to: e.g, Manufacturing process of the drug substance, Shelf-life changes including after first opening and reconstitution and its specifications, Storage conditions, Test procedures of active substance, medicinal product & non-pharmacopoeial excipients, Major change to the formulation, & packaging material, Change of name or code of IMPs etc** |
| **Any change that impacts on patient safety, quality or the analysis of data (major safety warning requires a new application (e.g study procedures, Reducing/increasing number of monitoring visits etc.)** |
| **Use of new measurements (methods) for the primary endpoint** |
| **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/s** |
| **Major change in objectives, endpoints and rationale of the study** |
| **Change in study design with impact on statistical analysis or the risk/benefit assessment** |

**SECTION 1: ADMINISTRATIVE**

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| **PART 1: ADMINISTRATIVE DETAILS** | |
| 1.1 Study Title |  |
| 1.2 Approved Protocol No, Date and Version |  |
| 1.3 Phase of trial |  |
| 1.4 Sponsor |  |
| 1.5 Applicant |  |
| 1.6 Date of approval of original protocol |  |
| 1.7 Details of investigators and sites already approved for this trial (Name of sites, investigators, Designation (whether Principal Investigators or Sub-Investigator). |  |
| 1.8 This Amendment No, Protocol Version No, and date of amendment\*. |  |
| 1.9 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 Current stage of the trial (E.g: Screening, Enrolling, Treatment phase, Follow-up) |  |
| 2.4 Number of participants currently enrolled |  |
| 2.5 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 form 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  ……………………………………. | |